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TABLE OF CONTENTS FIRST PAGE

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

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TABLE OF CONTENTS

ORIGINAL ARTICLES

PAGE

Staphylococcal Infections and the Problem of Antibiotic-Resistant Staphylococci

Wesley W. Spink, M.D., Minneapolis 167

Evaluation of Provocative Blood Enzyme Tests Employed in Diagnosis of Pancreatic Disease

David A. Dreiling, M.D., and Alexander Richman, M.D., with the Technical Assistance of Miss Alice Klein, A.B., New York 197

Clinical Experience with Coumarin Anticoagulants Warfarin and Warfarin Sodium

Dallas V. Clatanoff, M.D.; Perry O. Triggs, M.D., and Ovid O. Meyer, M.D., Madison, Wis. 213

Porphyria

Gabriel A. Schwarz, M.D., Philadelphia, and James A. L. Moulton, M.D., Cincinnati ... 221

Roentgen Changes Observed in Generalized Scleroderma

Joseph A. Boyd, M.D.; Simmons I. Patrick, M.D., and Robert J. Reeves, M.D., Durham, N. C. 248

Dangerous Cardiac Effects of Tetraethylthiuram Disulfide (Antabuse) Therapy in Alcoholism

Edward S. McCabe, M.D., and William W. Wilson, M.D., Philadelphia 259

Periarteritis (Polyarteritis) Nodosa Producing Intussusception

Hyman J. Zimmerman, M.D., Chicago; William P. Kleitsch, M.D.; Arthur M. Greene, M.D., and Harry F. McFadden Jr., M.D., Omaha 264

PROGRESS IN INTERNAL MEDICINE

Infectious Diseases

Hobart A. Reimann, M.D., Beirut, Lebanon 272

CASE REPORTS

Extrarenal Hypernephroma

Aaron Weisberg, M.D., and George Strenger, M.D., Brooklyn 314

Thrombocytopenic Purpura Associated with Cat-Scratch Disease

Joseph P. Belber, M.D.; Aaron E. Davis, M.D., and Ervin H. Epstein, M.D., Oakland, Calif. 321

Acute Adrenal Insufficiency

Walter A. Keitzer, M.D., and Paul E. Cheek, M.D., Akron, Ohio 326

REGULAR DEPARTMENTS

Books 328

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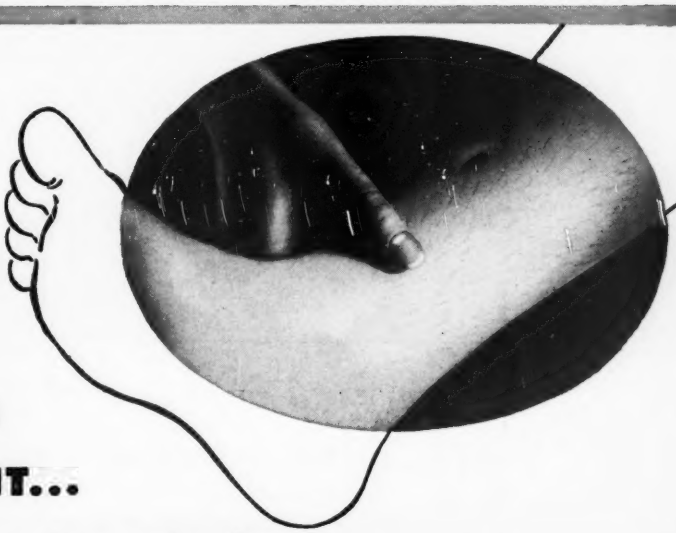

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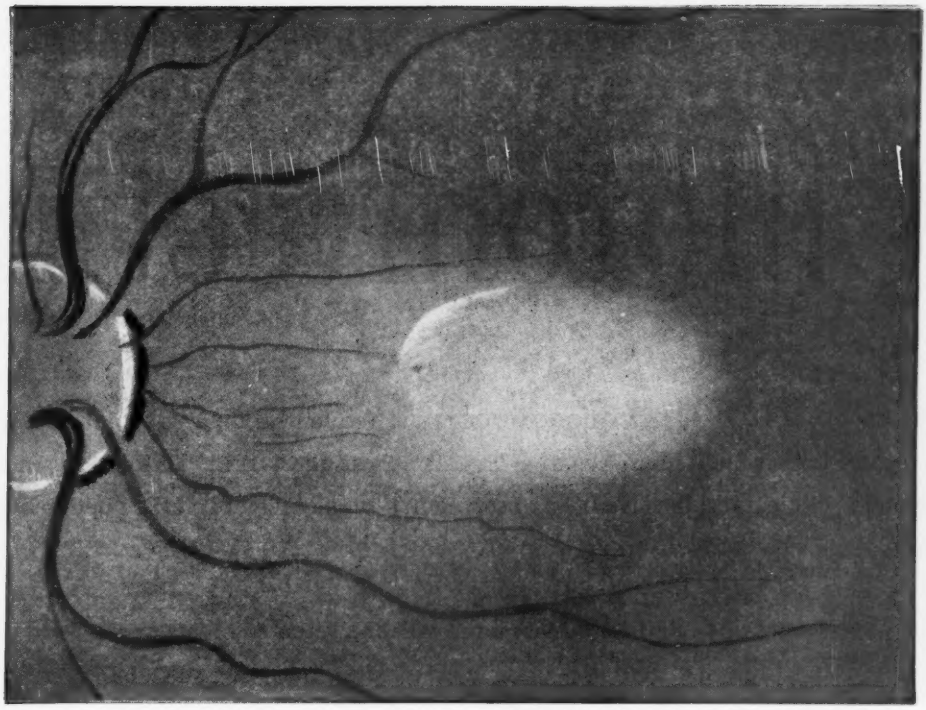

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STAPHYLOCOCCAL INFECTIONS AND THE PROBLEM OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

WESLEY W. SPINK, M.D.
MINNEAPOLIS

PENICILLIN was injected for the first time into a human patient having an infection on Feb. 12, 1941.[37] The patient had severe staphylococcal sepsis and improved considerably, but he died subsequently because of the very limited supply of penicillin. Shortly thereafter, with more antibiotic available, penicillin proved to be extraordinarily effective for the treatment of staphylococcal disease. As a consequence, the mortality rate for staphylococcal septicemia was sharply reduced, and chronic debilitating disease was decreased in those who recovered. But within a decade penicillin was to lose much of its therapeutic effectiveness for staphylococcal sepsis, and, regardless of the advancements made with other antibiotics, the mortality rates from staphylococcal septicemia in many clinics today approach and even surpass 50% of the cases. Many of the disappointing clinical results with penicillin and other antibiotics have been due to the appearance of strains of staphylococci resistant to the antibacterial action of the drugs. After the introduction of each antibiotic staphylococci have exhibited this property of resistance. While other species of bacteria have demonstrated resistance to some of the antibiotics, the Staphylococcus has been the most consistent in exhibiting prompt resistance to each of the antibiotics, and infections due to this species pose the most serious clinical problem of antibiotic resistance today.

The purpose of this report, prepared primarily for clinical application, is to review briefly the host-parasite relationships in staphylococcal infections; the epidemiological characteristics of the disease; the changing clinical pattern of severe staphylococcal sepsis from the presulfonamide era up to the present day of multiple antibiotics; the basic factors underlying the resistance of staphylococci to the sulfonamides and to the antibiotics, along with the epidemiological and clinical implications of this bacterial resistance, and, finally, the present day management of staphylococcal infections.

THE STAPHYLOCOCCUS (MICROCOCCUS PYOGENES VAR. AUREUS)

Information concerning the classification and growth requirements of staphylococci can be obtained from any standard textbook of bacteriology or laboratory manual, and, if more extensive surveys are desired, the reviews of Blair * and others [124] can be consulted. Staphylococci abound freely in the immediate environment of man. As a result, this species is a frequent contaminant of culture media. The problem often confronting the clinician is the significance of staphylococci

Professor of Medicine, University of Minnesota Medical School.

* References 11 and 12.

isolated from cultures of exudates or body fluids obtained from febrile patients. How can saprophytes be differentiated from pathogenic staphylococci? A universal, but at times erroneous, differentiation is based upon the appearance of colonies of Staphylococcus on blood agar plates. Orange colonies surrounded by a zone of hemolysis are looked upon as pathogenic organisms, while white colonies displaying no evidence of hemolysis are often considered to be nonpathogenic. The latter cultures are often put aside and labeled as contaminants. In general, this is a correct interpretation. But highly invasive strains of staphylococci may grow as white, nonhemolytic colonies. The coagulase test provides a simple and practical method for differentiating pathogenic from nonpathogenic strains of Staphylococcus and is performed by adding staphylococci to fresh human or rabbit plasma. A loopful of organisms from a 24-hour culture is added to 0.5 ml. of a 1:10 dilution of human plasma contained in a small tube. After three to eight hours of incubation at 37 C. a coagulum will be formed with pathogenic strains but not with nonpathogenic organisms. A more rapid procedure involves the use of a rapid slide test.[80] The basis of the reaction resides in an antigenic factor produced by pathogenic strains, which, through the intermediary of a plasma activator, causes the clotting of fibrinogen.† While the coagulase test provides a simple method for screening strains of Staphylococcus for pathogenicity, an occasional pathogenic strain may display a doubtful or negative test. Some cultures apparently contain a mixture of coagulase-positive and coagulase-negative variants, and the results of a test may depend upon the preponderance of one or the other of these variants.[103] The precise role of coagulase in the pathogenesis of staphylococcal infections is not known. Coagulase-positive strains resist the killing effect of fresh human blood, while coagulase-negative staphylococci are killed in large numbers.[109]

Extracellular substances that are of clinical importance are elaborated by some pathogenic strains of Staphylococcus. The most devastating of these exotoxins is lethal toxin, which may provoke fatal circulatory and respiratory failure. Attention was dramatically focused on this toxin after the Bundaberg disaster, of 1928.[56] In this community of Queensland, Australia, 21 small children were injected with diphtheria toxin-antitoxin that had been contained in a bottle free of antiseptic and contaminated with a strain of Staphylococcus that produced lethal toxin. Within 48 hours after inoculation, 12 of the 21 children were dead because of the action of the staphylococcal lethal toxin. This staphylococcal toxin is antigenic, and an effective antitoxin can be prepared against it. The same exotoxin that causes death may produce severe necrosis of the skin and has been called dermonecrotoxin. Stookey and his associates [112] called attention to patients with erysipelas who had as a complication necrotizing ulcers caused by staphylococci that produced this toxin. The hemolysins generated by some strains are probably of minor clinical importance. But of major clinical and epidemiological significance are those strains that produce enterotoxin.[20] This toxin causes an acute diarrhea and is one of the commonest causes of food poisoning. Extracellular filtrates of staphylococcal cultures may also contain other factors, such as leucocidin, which destroys leucocytes; hyaluronidase, or spreading factor, and fibrinolysin, which lyses fibrin. Rarely, a strain of Staphylococcus may cause a rash indistinguishable from that of scarlet

† References 55 and 86.

fever. The erythrogenic toxin produced by the offending Staphylococcus is antigenically the same as that formed by Group A hemolytic streptococci, and streptococcal antitoxin can neutralize the staphylococcal erythrogenic toxin.[1]

EPIDEMIOLOGY

The major human reservoirs of staphylococci are the nasopharynx and the skin. Miles and his associates [78] cultured Staphylococcus aureus from the anterior nares in approximately 50% of healthy adults, and from the skin of the wrist in almost 20% of these persons. The immediate environment of carriers, including their clothing and the air, is readily contaminated by staphylococci. Duguid and Wallace [30] showed experimentally that the air adjacent to nasal carriers was more heavily contaminated through the liberation of dust from their clothing than that which followed sneezing. Studies have demonstrated how quickly the nasopharynx

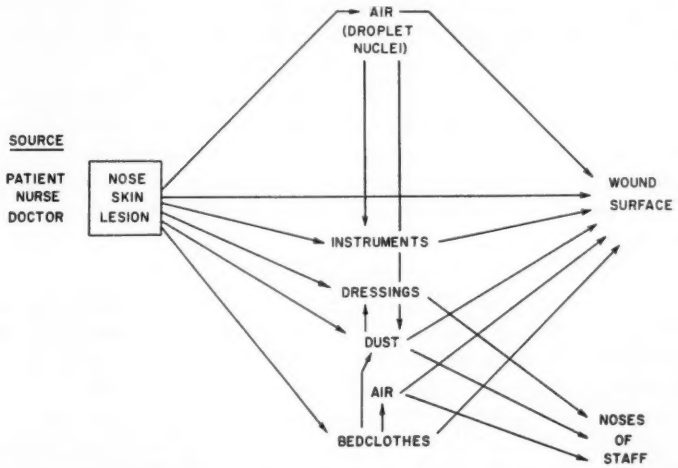

Fig. 1.—Sources of staphylococci and pathways whereby wounds become infected and new carriers become established. Courtesy of P. M. Rountree: Cross Infection of Surgical Wounds, *M. J. Australia* **2**:766, 1951.

of newborn babies in maternity hospitals can become parasitized by staphylococci.‡ It was observed in Australia that 90% of the babies can become heavy nasal carriers within seven days. Bacteriophage typing indicated that only a very small percentage of the infants were carrying the same types as the mothers. Large numbers of staphylococci, which were of the same types as were found in the babies, were found in the air of the nursery and in the nares of the nurses. Very similar studies were reported from England, with the additional fact that 90% of the infant carriers harbored penicillin-resistant staphylococci.

Since staphylococci are found in abundance on the skin and clothing and in the air and since the organisms are quite hardy, remaining viable under varying changes in environment, it is readily understood why the skin and adjacent tissues frequently become infected with this species of bacteria.[121] Clean surgical wounds

‡ References 10 and 94.

are often infected by staphylococci, which may lead to disastrous results. While the air of an operating room can become contaminated from the staphylococci in the nasopharynges of the nursing and surgical staff, Devenish and Miles [24] have offered evidence that a majority of the infections are due to the puncture of the rubber gloves of the surgeons and the leakage of staphylococci through the accumulated perspiration. They found the frequency of glove puncture during an operation to be as high as 24%. The possible sources of wound infections have been diagrammed by Rountree,[93] and a reproduction is presented in Figure 1. She has emphasized the contamination of the air in hospital wards in making up the beds and in shaking out the blankets.

A major cause of food poisoning, if not the commonest cause, is the contamination of food by staphylococci that produce enterotoxin. Outbreaks of this type of staphylococcal poisoning usually occur in groups who have partaken of food prepared several hours before it is eaten, and the foods include salads, meat pies, cream cakes, custards, and sandwiches. Staphylococci are introduced by the food handlers, and a suitable period of incubation permits the formation of toxin by the staphylococci, which is then ingested in the food by the diners.

Advancements in our knowledge of the epidemiology of staphylococcal diseases have been brought about through the identification of various strains of pathogenic Staphylococcus by means of bacteriophage typing.§ While only 50 to 75% of the strains at present are typeable, the procedure has been extremely helpful in studying the problem of the epidemiology of antibiotic-resistant staphylococci, to be discussed shortly.

RESPONSE OF HOST TO STAPHYLOCOCCUS

There are two characteristic features of the reaction of the tissues to staphylococci, both of which are concerned in the local defense mechanism of the host. First, localization of the organisms at the portal of entry is attempted, as reflected in the mobilizing of polymorphonuclear leucocytes and the formation of an abscess, with destruction of the tissues. Phagocytosis of the staphylococci occurs. Second, a vascular reaction takes place, with thrombosis of vessels being particularly prominent. The thrombosis leads to the ischemia of tissues, then to necrosis, and, with organisms present, abscess formation takes place. These infected thrombotic areas serve as foci for the seeding of the blood stream and the localization of the staphylococci elsewhere in the body. This has been termed pyemia, and it is in this manner that multiple metastatic bacterial lesions occur in the body. Localization of the staphylococci commonly occurs in the long bones, resulting in osteomyelitis. Other vulnerable sites include the kidneys, endocardium, lungs, meninges, brain, liver, and spleen. Unless the defense mechanism of the host, with or without the aid of antibiotic therapy, prevents the multiplication of staphylococci and unless suppurative areas are absorbed or drained surgically, chronic and disabling disease or death may ensue.

Not only does localization of the staphylococci occur, resulting in the necrosis of tissues and formation of abscesses, but, on occasion, a severe state of toxemia may take place because of the elaboration and dissemination of exotoxin. The devastating and rapidly fatal effect of lethal toxin is shown in Figure 2. A healthy young adult suffered a minor laceration of the skin, which became infected with

§ References 13 and 122.

a strain of Staphylococcus that produced exotoxin. Although successful localization of the bacterial cells occurred without invasion of the bloodstream, exotoxin formed locally, entered the blood stream, and caused death within 51 hours. The sequence of clinical events four hours after the accident is also shown in the chart. Postmortem studies revealed congestion of the viscera and organs, but there was no inflammatory reaction of the tissues, except at the primary site in the skin. A second case can be cited in which a fulminating and lethal outcome occurred, which was associated with a rapidly progressive necrosis of the skin. A debilitated cardiac patient had the acute onset of bullous lesions of the upper part of the leg, which coalesced and had a circumscribed erythematous border. This was quickly followed by a dry necrosis of the skin, with involvement of the entire leg. The whole area became black. Staphylococci were isolated from the bullae. The lesion that resulted is shown in Figure 3. This same type of ischemic necrosis may be pro-

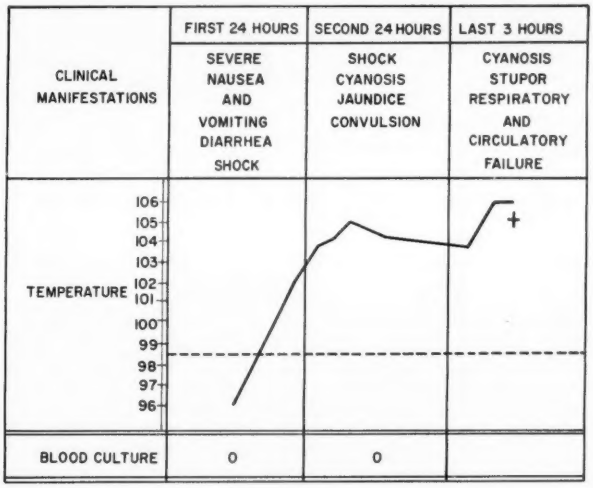

Fig. 2.—Clinical course of patient with fulminating and fatal staphylococcal infection in which death was due to lethal staphylococcal toxin. Entire course was only 51 hours. Note absence of bacteremia.

duced experimentally in the rabbit's skin. Figure 4 demonstrates extensive necrosis of the abdominal tissues of a rabbit following the local injection of a strain of Staphylococcus that produced dermonecrotoxin.

Although considerable information is available concerning the metabolic activities of the Staphylococcus and the histopathology of the tissue reactions that this species induces, there is a paucity of knowledge on the nature of the defense mechanism or mechanisms of the host. Few reliable data are at hand relating to antibacterial immunity. Why are some persons, notably diabetics, more prone to acquire staphylococcal sepsis than nondiabetics? Why do some persons have recurrent furunculosis? These and other questions can be answered only after a more intensive study of the host-parasite relationship. Recent investigations have centered around the well-recognized phenomenon of the phagocytosis of staphylococci, with particular reference to the role of the polymorphonuclear leucocytes.

It is generally accepted that Gram-positive bacteria, including staphylococci, are ingested and destroyed by phagocytes. Since tremendous numbers of polymorphonuclear leucocytes swarm around staphylococci shortly after the invasion of the tissues, the leucocytes must be very important in localizing and even destroying

Fig. 3.—Necrotic lesion of leg from fatal case of staphylococcal sepsis in which strain of Staphylococcus produced dermonecrotoxin. Courtesy of Dr. Wendell H. Hall.

Fig. 4.—Extensive necrosis of abdominal wall of rabbit following intradermal injection of staphylococcal dermonecrotoxin. Courtesy of Dr. A. Thal, Department of Surgery, University of Minnesota Medical School.

the organisms. That phagocytosis of staphylococci by polymorphonuclear leucocytes may have certain shortcomings unfavorable to the host has been suggested by Rogers and Tompsett,[92] who demonstrated in vitro that coagulase-negative (nonpathogenic) staphylococci did not survive within the leucocytes but that survival of coagulase-positive (pathogenic) staphylococci took place within these cells.

Thus phagocytosis may be a double-edged sword as far as the host is concerned. It is favorable to the host when bacteria are localized and dissemination of the infection is prevented. Phagocytosis may be unfavorable if the microbes survive within the cells. In this position the bacteria may be protected against humoral antibodies of the host and against antistaphylococcal drugs, which has been demonstrated experimentally for Brucella organisms and for tubercle bacilli.||

Additional investigations are beginning to shed some light on the problem as to why persons with diabetes are more susceptible to staphylococci than are normal persons. The fundamental approach to this problem by Dubos [29] is intriguing. Acting upon the hypothesis that the internal environment of the phagocyte is unfavorable for the ingested staphylococci because of the formation of lactic acid, he proceeded to observe the influence of ketone bodies upon the antibacterial effect of lactic acid. Using balanced media, he showed that in the presence of ketone bodies the bacteriostatic and bactericidal activities of lactic acid were decreased. Under certain conditions, then, lactic acid was unfavorable for the survival of staphylococci, whereas ketone bodies favored survival. Martin and his associates [73] have reported results on the metabolic functions of polymorphonuclear leucocytes from diabetic patients and from normal controls that supplement the studies of Dubos by showing that leucocytes from normal persons produce more lactic acid from glucose than do those from diabetics. Furthermore, in the presence of insulin the diabetic's leucocytes formed more lactic acid than did the normal person's leucocytes with insulin. The foregoing observations suggest quite strongly that ketosis may interfere with the defense mechanism through alteration in the internal metabolism of the phagocyte.

Further fundamental investigations concerning the metabolism of the host's cells are badly needed for a more precise understanding of the host-parasite relationship in staphylococcal disease. It would be interesting, and perhaps profitable, to study humoral antistaphylococcal factors in those persons with agammaglobulinemia.[17] Because of this deficiency, little or no gamma globulin is formed, which is reflected in the absence of circulating antibodies.

SOME TRENDS IN OUTCOME OF PATIENTS WITH STAPHYLOCOCCAL INFECTIONS

For a period of 20 years I have made clinical observations on the changing pattern of staphylococcal infections. Interest in this aspect of infectious diseases was first aroused on the wards of the Boston City Hospital, in 1933. Over the intervening years dramatic changes in the management and outcome of patients with staphylococcal sepsis have taken place through the successive introduction of therapeutic agents. In an attempt to evaluate clinically any therapeutic advancements, one could attempt a rough measurement of the results in the management of two severe manifestations of staphylococcal disease—septicemia and osteomyelitis. To accomplish this the two decades (1933-1953) may be divided into these four periods:

1. The presulfonamide period..... 1933-1936
2. The sulfonamide period..... 1937-1941
3. The penicillin period..... 1942-1947
4. Multiple antibiotic period..... 1948-1953

|| References 71, 72, 100, and 114.

Every clinician who worked in a general hospital prior to 1937 will remember vividly the many patients with staphylococcal osteomyelitis who occupied hospital beds. The disease was chronic, debilitating, and disabling and was prone to recur. The mortality rate was not insignificant, especially in adults. But even more discouraging was the fatal outcome in the majority of patients with staphylococcal septicemia. The over-all mortality rate of staphylococcal septicemia in several clinics was greater than 80%.¶ Sulfanilamide was introduced for general use in 1937, but disappointing results were obtained in cases with severe staphylococcal sepsis. More encouraging benefits appeared to be related to the use of sulfapyridine and, especially, sulfathiazole.# The thiazole derivatives of sulfanilamide were effective in acute urinary tract infections, and the mortality rates of small groups of cases of staphylococcal bacteremia were reduced. The report of Spink and his associates [108] on the results with sulfathiazole in staphylococcal bacteremia was quite encouraging, but several of the cases treated were only of moderate severity. Subsequent results in the same clinic with severe cases of septicemia were much less satisfactory.

While only limited supplies of penicillin were available in 1942, the early enthusiasm of the Oxford investigators soon became apparent in many other clinics. In the clinical material available at the University of Minnesota, 28 patients with staphylococcemia received penicillin between 1942 and 1944, and the mortality rate was 28%.[46] This was a precipitous drop from the prepenicillin rate, of over 80%. It is remarkable, in view of the excellent clinical results that were being obtained with penicillin, that a cautious note concerning the problem of penicillin-resistant staphylococci as a cause of therapeutic failure was introduced as early as 1942, when Rammelkamp and Maxon [88] suggested that failure in one case was associated with the appearance of resistant staphylococci. Such a sequence of events was reported later by others.* Within five years after its introduction, many therapeutic failures were associated with infections due to penicillin-resistant strains of Staphylococcus. Other antibiotics then became available for staphylococcal sepsis, and streptomycin was employed, particularly in those instances in which penicillin-resistant staphylococci were involved. Again failure was encountered because of the appearance of highly resistant organisms in a very short period of time. In 1948, chlortetracycline (Aureomycin) was used in cases having penicillin-resistant staphylococci, and successful results were reported.[81] Similar results were obtained with oxytetracycline (Terramycin). But resistance to the tetracyclines also became a serious stumbling block in therapy. Chloramphenicol (Chloromycetin) has not been widely used for staphylococcal sepsis. Erythromycin was then advocated for the therapy of antibiotic-resistant strains of Staphylococcus, but therapeutic failures are now being encountered because of the appearance of erythromycin-resistant staphylococci. Finally, the potentially toxic antibiotics, bacitracin and neomycin, have been offered for the therapy of patients infected with staphylococci resistant to the other antibiotics.†

By the judicious use of large amounts of penicillin and other antibiotics, some remarkably good therapeutic results have been reported in the treatment of staphylo-

¶ References 77, 102, and 113.
# References 48 and 87.
* References 41 and 106.
† References 75 and 90.

coccal endocarditis.[26] In general, the appearance and dissemination of antibiotic-resistant strains of Staphylococcus is being associated not only with a rising incidence of therapeutic failures but also with an increase in the mortality rates of patients with staphylococcal septicemia. Beginning in 1952 and continuing through 1953 the mortality rate from the infection in patients in the clinics of the University of Minnesota has been approximately 50%. This means that, regardless of the advances that have been made in the management of patients with antibacterial agents, a patient with staphylococcal septicemia has only a 50-50 chance of surviving in a large university clinic. While severe staphylococcal sepsis is a challenging problem in many large medical centers, there does not appear to be a significant increase in the incidence of chronic osteomyelitis.

CHANGING PATTERN OF SULFONAMIDE- AND ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

Significant information is now available in which the rising incidence of staphylococcal disease in general hospitals and the failure of the patients to respond to treatment can be related to the appearance of strains of Staphylococcus resistant

TABLE 1.—*In Vitro Sensitivity of Sixty-Seven Strains of Coagulase-Positive Staphylococcus to Penicillin, Which Had Been Isolated Prior to Introduction of Penicillin*

Strains, No.	Concentration of Penicillin Inhibiting Growth, Oxford Units/Ml.
12	0.05
25	0.1
22	0.2
1	0.4
5	0.6
2	0.8

to the antibacterial activity of therapeutic agents. This aspect of chemotherapy has been the subject of investigation in our laboratory and clinics at the University of Minnesota Hospitals for several years. Shortly after sulfanilamide became available for general use, we observed that the vast majority of strains of Staphylococcus were sensitive in vitro to this drug, but as time elapsed and as sulfanilamide and its derivatives were more widely administered an increasing number of sulfonamide-resistant strains of Staphylococcus were detected.‡ It is appreciated that the sulfonamides were not too effective initially for staphylococcal infections, with but few exceptions. One of the exceptions was in the treatment of acute urinary tract infections. Sulfonamide preparations, especially sulfathiazole, did control this disease in many instances. But with the appearance of resistant staphylococci, this beneficial effect correspondingly decreased. It was anticipated that a similar sequence of events might occur with penicillin. Fortunately, a large number of coagulase-positive strains of Staphylococcus had been acquired from patients prior to the introduction of penicillin, and the results of in vitro sensitivity tests with these strains could be employed as a base line for comparison with results on strains isolated in succeeding years.[106] Another fortunate factor in these comparative studies is that essentially the same type of in vitro sensitivity test has been used

‡ References 110 and 117.

in the laboratory over a period of several years. Table 1 shows the results of sensitivity tests with 67 strains of coagulase-positive Staphylococcus that had been isolated from patients prior to 1940, and hence it is assumed that these organisms had not been exposed to penicillin. While some differences in sensitivity are apparent, the significant feature is that none of the strains required more than 1 Oxford unit of penicillin to inhibit growth. In fact, after penicillin had been used for two years at the University of Minnesota Hospitals the statement was made that penicillin-resistant staphylococci did not pose a serious therapeutic problem.[107] But within five years the whole picture was to change. A subsequent report, in 1951, revealed that approximately 50% of the strains being isolated from patients were highly resistant not only to penicillin but to streptomycin as well.[104] At that time the same strains were found to be quite susceptible to the action of chlortetracycline, oxytetracycline, and chloramphenicol. As the human population became exposed to new antibiotics, the picture changed again, and by the end of 1953

TABLE 2.—*In Vitro Sensitivity of Strains of Staphylococcus to Antibiotics in a General Hospital over a Three-Year Period*

	1951			1952			1953		
	Strains Tested, Total	> 50 Units or γ Required to Inhibit Growth		Strains Tested, Total	> 50 Units or γ Required to Inhibit Growth		Strains Tested, Total	> 50 Units or γ Required to Inhibit Growth	
	No.	No.	%	No.	No.	%	No.	No.	%
Penicillin	48	30	62.5	42	24	57.2	153	96	62.7
Streptomycin	48	23	48.0	41	20	48.8	153	100	65.3
Chlortetracycline	48	11	23.0	42	14	33.2	153	96	62.7
Oxytetracycline	42	16	38.0	40	19	47.5	153	96	62.7
Chloramphenicol	48	12	25.0	40	1	2.5	153	1	0.65
Erythromycin	..	..	....	30	0	0	153	28*	18.3
Carbomycin	..	..	....	..	..	....	153	28	18.3
Bacitracin	20	0	0	26	0	0	153	0	0
Neomycin	12	0	0	24	1	4.2	153	0	0

* Eleven since Oct. 13, 1953.

strains in considerable numbers were being isolated that were resistant to chlortetracycline, oxytetracycline, erythromycin, and carbomycin (Magnamycin). The magnitude of the problem is reflected in the data presented in Table 2.§ Of particular interest are the results with erythromycin. During 1952, when the drug was first introduced, no resistant strains were encountered. But as erythromycin was used more extensively, resistant strains appeared. Similar observations have been made by others.[67] In contrast with the results with erythromycin and the other antibiotics commonly used for staphylococcal infections, it is noted that chloramphenicol-resistant strains were encountered infrequently. This is probably related to the fact that this drug has not been widely used in the community. This statement can also be applied, in part, to the results obtained with neomycin and bacitracin.

The foregoing observations indicate that when a sulfonamide or an antibiotic is used promiscuously and intensively in a community, resistant strains of Staphylococcus will make their appearance and parasitize a significant segment of the population. Such results have been reported by others in the United States, notably

§ These studies were carried out by Miss May V. Collin.

by workers at the Mayo Clinic ||; by Finland and his associates,[35] at the Boston City Hospital; by Knight and Holzer,[60] in New York; by Dowling and his group,¶ in Chicago, and by Kirby and his associates,[59] in Seattle. Leyton [69] has made comparable studies in Winnipeg. Barber,# in England, and Rountree,* in Australia, have carried out excellent investigations on the epidemiology of resistant staphylococci, particularly with reference to penicillin-resistant strains, and their results are in accord with those of others.

SOME BASIC PRINCIPLES RELATED TO APPEARANCE OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

The appearance and wide dissemination of penicillin-resistant staphylococci is unique in that no other species of micro-organisms has posed such a major problem in clinical medicine. This species has manifested resistance not only against penicillin but against several other antibiotics as well. This phenomenon has excited the interest of investigators in the different fields of the biological sciences, including genetics, microbiology, and biological chemistry. Each of these groups, utilizing the tools of its discipline, has attacked what has turned out to be a very complicated problem. The Staphylococcus is a complex unicellular organism. For example, its nitrogen requirements for growth are dependent upon at least 17 amino acids plus thiamine chloride and nicotinamide.[44] But this same cell can synthesize ascorbic acid. The adaptability of the Staphylococcus is so elastic that by a process of nutritional attrition it can be trained to synthesize its own amino acids for protein requirements from a few simple salts. It is no wonder that a simple or single explanation cannot be forthcoming as to why the Staphylococcus exhibits resistance to an antibiotic. There are probably several different mechanisms involved. The unfortunate aspect of much of the work on bacterial resistance in general is that investigators have applied the tools and analytical methods of their own disciplines to perhaps one or, at most, a few strains of bacteria within a single species and then have made statements concerning the general problem of resistance from the few facts that they have elicited. This has demonstrated a gross and absurd violation of inductive reasoning and has been quite misleading to many, especially to the clinician.

Bacterial resistance to the sulfonamides and to the antibiotics is an expression of a universal phenomenon of life and can be best expressed in the one word, *adaptation,* used in its widest biological connotation. Every living organism, from the unicellular Staphylococcus to man, is constantly adapting itself to its environment. Failure to adjust to the rigors of a changing environment means destruction for the organism, and survival means that latent reserves have been successfully called up in the struggle. In the case of the Staphylococcus, survival in the face of a destructive agent like penicillin may require calling upon different metabolic pathways for its nutritional requirements. This struggle for survival is an expression of Darwin's "survival of the fittest"—a survival dependent upon several, but latent, metabolic alternatives. Bacterial resistance may be explained, in part at least, by applying the principles of organic evolution to the phenomenon.

|| References 50 and 81.
¶ References 27 and 67.
# References 5 and 9.
* References 96 and 97.

This means that in a large population of staphylococcal cells, the physical or metabolic endowment of some of the cells is such that survival is possible when the population as a whole is subjected to a destructive agent in the environment. These endowed cells are genetically constituted to reproduce in the face of a factor or factors that are lethal for the vast majority of the cells. This represents an orderly natural selection of resistant cells in response to the environment. Penicillin selects out those cells that are resistant, permitting them to reproduce, while the sensitive cells perish. On the other hand, if the hypothesis of organic evolution is pushed still further, this need not be an orderly selective process operating only when the cells are exposed to penicillin, but resistant cells within a bacterial population may arise spontaneously through mutation and proliferate in the absence of penicillin. This latter explanation may apply to those strains that are resistant to penicillin even though there is no evidence that the population had ever come in contact with the antibiotic.

Since the predication is being made that bacterial resistance rests upon a genetic basis, it is well to review briefly the principles of heredity and then search for evidence that they apply to the bacterial cell. Contained within the nucleus of the cell are chromosomes, which determine the characteristics of that cell and which through chemical reactions result in growth and division of the cell. Chromosomes are composed of protein plus deoxyribonucleic acid (DNA). Within the chromosomes are genes, which probably are protein molecules that control inherited traits through chemical processes. A mutant represents a change in the molecular structure of the gene, which in turn results in changes in the chemical function or activity of the cell. Reproduction on a genetic basis may occur through a sexual phase in which two germ cells are involved or the nuclei of two cells fuse. Or an asexual phase may take place, in which there is simple division of the cell, or fission. There is now evidence at hand to indicate that bacterial cells do possess nuclei and that DNA is a definitive factor in the hereditary transmission of characteristics by these cells.† And in an interesting and provocative review on "Sex in Bacteria," Lederberg and Tatum [65] have illustrated the role of genes in the bacterial cell. Evidence that these genetic factors in bacteria are responsible for antibiotic-resistant strains will be discussed shortly.

Another explanation offered for the appearance of antibiotic-resistant bacteria is that, in response to the antibacterial activity of the antibiotic, the micro-organisms adapt metabolically, perhaps on the basis of enzyme function, so that the bacterial cells circumvent the deleterious activity of the antibiotic. Such adaptation is temporary, usually enduring as long as the organisms are in contact with the antibiotic, and is not transmissible from cell to cell along genetic lines. Evidence will be presented subsequently for this hypothesis.

In summary, then, there are at least four possible mechanisms to explain the appearance of resistant micro-organisms, as follows: 1. Mutants may appear spontaneously in a bacterial population that are resistant to the destructive action of a given antibiotic. These resistant cells arise and reproduce totally independently of the presence or absence of the antibiotic. 2. A large bacterial population can contain a rare mutant or mutants possessed with the property of resisting the action of an antibiotic. The antibiotic selects out and kills the preponderantly

† References 4, 14, 28, and 63.

sensitive cells, permitting the resistant cells the opportunity to reproduce and to present eventually a uniformly resistant culture. 3. Bacterial resistance is not dependent upon genetic factors, but it represents through enzymatic activity a temporary metabolic adjustment to an unfavorable environment. This may include morphological changes, as well as functional adaptation. 4. The complex picture of bacterial resistance can best be explained by combining all of the three foregoing hypotheses.

Some of the evidence for each of the four possibilities will now be presented, particularly with reference to the Staphylococcus. Consideration will be given to the first two possibilities, wherein a population of bacterial cells contains resistant mutants that may proliferate rapidly, either spontaneously or with the aid of the selective action of the antibiotic. Lankford and his associates [62] were among the first to study this problem, and after an in vitro investigation of the effect of sulfonamides on 100 strains of Neisseria gonorrheae they stated that "sulfonamide-resistance is a sudden spontaneous 'mutation,' occurring continuously, but becoming evident only when conditions are suitable for selective propagation of the resistant variant cells." Oakberg and Luria,[83] utilizing the fluctuation test of Luria and Delbrueck,[70] reported that sulfonamide-resistant staphylococci appeared as a result of mutations, and Demerec [23] demonstrated a similar sequence of events for penicillin-resistant staphylococci. Independently, Kirby [57] showed that penicillin selected out penicillinase-producing, resistant staphylococci, which was soon confirmed by others.[41] That antibiotic-resistant mutants exist in a population made up primarily of sensitive cells and that these resistant cells can be selected out quite independently of the antibiotic has been demonstrated by the replica-plating method of Lederberg.[64]

There is also experimental evidence that staphylococci may display a temporary type of acquired resistance to penicillin quite divorced from the more stable inheritable mechanism.‡ By exposing a penicillin-sensitive culture of Staphylococcus in vitro to increasing concentrations of penicillin, a strain can be made to resist successfully the antistaphylococcal action of high concentrations of the antibiotic. But when this resistant culture is grown in the absence of penicillin for a few generations, sensitivity to penicillin is restored to the progeny. From a clinical and epidemiological point of view, this form of temporary penicillin resistance is of minor importance.

There are, then, at least two main types of penicillin-resistance for staphylococci. The first type is of a temporary, noninheritable nature, and the second is a more stable and inheritable form of resistance. The latter type is of major importance to the clinician and involves strains containing penicillinase-producing mutants, which, after several generations, can displace the more sensitive cells, with a stable and highly resistant culture as a result. These strains of staphylococci have an enzyme, penicillinase, which inactivates penicillin. Penicillin-resistant staphylococci isolated from human beings are practically always penicillinase-producing strains. Failure to distinguish between these two fundamentally different mechanisms has caused considerable confusion. Gale [39] has attempted to explain the basic chemical activity that distinguishes penicillin-resistant staphylococci from sensitive strains, but his comparisons were carried out with cultures that possessed the temporary type of resistance. His final conclusions defining the metabolism of penicillin-

‡ References 105 and 116.

resistant staphylococci do not apply to the more important penicillinase-producing strains.§ However, the temporary or acquired type of resistance is of further interest because of the varied alterations in morphology and metabolism that the resistant cocci may manifest, and these changes are of some clinical significance. Barber [6] has shown that penicillin-dependent variants can be isolated under experimental conditions, in which the cocci grow only in the presence of the antibiotic. Whether this has any clinical importance has not been established, but Hall and Spink [47] have isolated streptomycin-dependent Brucella cells from the blood of a patient who received streptomycin for brucellosis. In the presence of penicillin and other antibiotics, minute colonies of staphylococci, or G forms, may appear. Not only has this been demonstrated experimentally, but such cultures have been isolated from human patients undergoing treatment.|| In the absence of the antibiotic these small colonies revert back to large colonies of virulent staphylococci. The clinical application of this phenomenon is that G colonies are so small that cultures of exudates or body fluids containing these forms may be overlooked on media, and the culture will be reported as sterile. Small-colony forms of Escherichia coli have been isolated from the urine, and L forms have been produced in abundance by exposing Salmonella typhimurium and Hemophilus influenzae to penicillin or amino acids.¶

While the application of genetic concepts and methods to the study of sulfonamide- and antibiotic-resistant staphylococci has yielded valuable information, relatively meager knowledge is available in relation to the underlying chemical activities involved in resistance. It is well established that sulfonamide-resistant staphylococci synthesize *p*-aminobenzoic acid, which antagonizes the antibacterial action of the drugs.# But this is certainly only a partial explanation of the mechanism of sulfonamide resistance.* It is pretty well accepted that the activity of the enzyme penicillinase is of considerable significance in the resistance manifested by some strains of Staphylococcus to penicillin.[43] Studies with other bacterial species and antibiotics have suggested that antibiotic resistance may arise under some circumstances through bacterial transformation reactions in which hereditary characteristics are transmitted from one cell to another through the transmission of cellular factors, including deoxyribonucleic acid.† Another mechanism for the transference of hereditary factors is the transduction reaction, although it is less clearly understood.[128]

From our own experience, integrated with the observations of others, the basic principles underlying the appearance of antibiotic-resistant bacteria may be summarized, with particular attention given to resistant staphylococci. Extensive studies carried out with penicillin and resistant staphylococci have shown that no one mechanism is sufficient to explain the appearance of resistant bacteria. It is more likely that several mechanisms are involved, a concept which fits in with that of

§ Unpublished data from our laboratory show that the nitrogen requirements (amino acids) are just as exacting for highly resistant penicillinase-producing strains as for sensitive strains.

|| References 101 and 126.

¶ References 25 and 42.

References 61, 68, and 111.

* References 21 and 79.

† References 2, 3, and 51.

others.‡ A relatively stable and resistant culture of bacteria replaces an antibiotic-sensitive culture because the population of micro-organisms contains a few resistant mutants that reproduce rapidly, either spontaneously or as a result of the selective action of the antibiotic. In this case, resistance is a hereditary characteristic transmitted from cell to cell.

If resistant strains appeared spontaneously and absolutely independently of the antibiotic, then evidence should be at hand showing that such resistant strains had appeared before the antibiotics were ever used in clinical practice. It has been reported that an occasional strain of penicillin-resistant Staphylococcus did appear under these circumstances.§ Likewise, sulfonamide-resistant gonococci were isolated prior to the use of the sulfonamides.[98] However, our own experience leads us to believe that it was only an occasional culture of Staphylococcus that exhibited resistance to penicillin prior to the introduction of the antibiotic, as seen from the data in Table 1. This also applies to the sequence of events that has occurred with staphylococci and the other antibiotics. The vast majority of antibiotic-resistant strains of staphylococci have been selected out under the influence of an antibiotic. This explains the rapid rise of highly resistant cultures in the human population after the widespread use of an antibiotic. This problem applies particularly to the Staphylococcus.

There is also evidence that the appearance of resistant strains on a genetic basis occurs with only a selected few strains within a species. By means of bacteriophage typing of strains of Staphylococcus in various parts of the world it has been shown that the majority of the penicillin-resistant strains fall into Group III.‖ Our own experience fits in with this finding. We also believe that the resistant mutant of major importance is that cell endowed with the enzyme penicillinase. From the observations of Pollock [85] with Bacillus cereus, there exists the possibility that within a very few minutes after contact of these penicillinase-producing staphylococcal mutants with penicillin the production of penicillinase is accelerated considerably and that it remains at a high level after the penicillin is withdrawn. It should be emphasized, especially from the clinical viewpoint, that resistance of staphylococci to antibiotics is not of an absolute and fixed nature but that there are relative degrees of resistance. We have observed considerable variation in penicillin-sensitivity tests with those strains of Staphylococcus that require 50 units per milliliter or less to inhibit growth. We have concluded, without definitive evidence, that cultures displaying moderate degrees of resistance are probably composed of a mixture of sensitive and resistant organisms and that the predominance of either one or the other at a given time will determine the outcome of sensitivity tests. Barber [7] has brought forth some evidence supporting this concept. On the other hand, reversal of resistant strains of bacteria through a factor or factors transmitted by sensitive organisms of either the same species or unrelated species has been claimed.¶ When we have repeated sensitivity tests with subcultures of highly resistant strains of staphylococci the results have been quite constant. These strains grow in the presence of 500 to 1,000 units per milliliter of penicillin. We have been unable to reverse the resistance of these highly resistant penicillinase-

‡ References 8, 31, and 115.
§ References 60 and 99.
‖ References 13, 60, 91, and 123.
¶ References 118 and 125.

producing strains of staphylococci by exposing the cultures to either chlortetracycline or oxytetracycline.[18] Barber [7] has investigated this problem and has concluded that some penicillinase-producing strains will show a change in production of the enzyme after exposure to other antibiotics, but this variation is not due to a specific action on the production of penicillinase.

EPIDEMIOLOGY OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

If antibiotic-resistant strains of Staphylococcus appear as a result of a given antibiotic selecting out resistant variants or mutants from a sensitive culture, with the subsequent reproduction of the resistant cells at the expense of the sensitive organisms, then it could be anticipated that resistant strains would become established in patients and in a healthy human population where the antibiotic has been used extensively. Barber and Rozwadowska-Dowzenko,[9] in England, and North and Christie,[82] in Australia, were among the first to put forth this concept as an explanation for the increased incidence of penicillin-resistant staphylococci in a hospital population. Reference has already been made to the speed with which staphylococci can become established in the nasopharynges of newborn infants in hospital nurseries, including penicillin-resistant strains.# Rountree and her associates * have made some important epidemiological observations on the establishment and spread of antibiotic-resistant strains of Staphylococcus. By studying different population groups, they have demonstrated a close relationship between the incidence of resistant staphylococci and the use of the antibiotics. As an example, strains of Staphylococcus isolated in a hospital population showed a considerably higher incidence of penicillin-streptomycin resistance than those isolated from outpatient groups. Furthermore, a survey of the hospital staff in a Sydney, Australia, hospital revealed that 54.5% were carriers of Staph. pyogenes and that 8 out of every 10 carriers were harboring penicillin-resistant strains. While the incidence of isolates of resistant strains was on the increase in both hospital patients and hospital personnel, a low number of resistant strains were encountered in Red Cross blood donors from the outside. And, finally, within five weeks after first-year trainee nurses had entered upon work in the hospital, the nasal carrier rate rose from 52.6 to 71.4% in this group, with penicillin-resistant staphylococci isolated from 4.3% initially and from 32.1% at the end of that period.

Dowling and his associates † have carried out extensive epidemiological studies which substantiate the concept that the incidence of carrier rates and infections caused by antibiotic-resistant strains of Staphylococcus is related to the use of the antibiotics. One of their studies is of immediate interest in showing that the intensive use of erythromycin in the hospital was associated with a rising incidence of erythromycin-resistant strains and that when the use of the antibiotic was restricted there was a corresponding fall in the carrier rate of resistant strains within a few months.[67] Observations reported by Finland and Haight,[35] from the Boston City Hospital, showed a very low incidence of chloramphenicol-resistant strains of Staphylococcus, which were highly resistant to several of the other antibiotics, and they ascribed the low incidence of chloramphenicol-resistant staphylococci to the

References 10, 74, and 94.

* References 95-97.

† References 27 and 66.

limited use of that antibiotic. Other groups ‡ in this country and elsewhere have shown quite clearly that the rising incidence of antibiotic-resistant staphylococci in hospital populations is related to the use of the drugs. Our own observations in the clinics associated with the University of Minnesota is in accord with the foregoing results. Since hospital personnel do not confine their activities to a hospital environment, these persons do carry and disseminate antibiotic-resistant strains in their homes and among populations distant to the hospital. The problem of antibiotic-resistant staphylococci has its focus in the hospital, but there are also considerable amounts of antibiotics being used for patients in urban areas outside of the hospital. The problem of resistant strains thus becomes an ever expanding one.

CLINICAL PROBLEMS ARISING OUT OF APPEARANCE OF ANTIBIOTIC-RESISTANT STAPHYLOCOCCI

If there has been a dissemination of antibiotic-resistant staphylococci among the population, especially in hospital groups where the drugs have been used intensively, then a definite increase in the incidence of staphylococcal sepsis due to these resistant strains should have occurred. This is just what has been happening in our own clinical material and in that of others. The increase in the incidence of cases of severe staphylococcal sepsis with septicemia during 1952 and 1953 in the clinics of the University of Minnesota has been most disheartening. During this period the over-all mortality rate has been over 50%, and 90% in those cases have had acute bacterial endocarditis. An analysis of this high death rate has indicated several responsible factors, such as infections due to antibiotic-resistant staphylococci; delay in initiating treatment; selection of the wrong antibiotic or combination of antibiotics, and the presence of other debilitating conditions.

The problem of staphylococcal sepsis has been intensified in the larger general hospitals because of two major factors. First, up to 50% or more of the hospital staff may be carrying coagulase-positive strains of Staphylococcus, and the majority of these strains are resistant to one or more antibiotics. Cross infections are occurring with increasing frequency among the patients because of this factor. Contamination of postoperative wounds and of lacerations and burns with resistant staphylococci has been a serious problem. We have seen instances of fatal septicemia due to resistant staphylococci rising out of a thrombophlebitis of the brachial vein, which had been induced by an indwelling plastic tubing placed there for the administration of fluids by a continuous intravenous drip. The results of properly timed and well-executed surgical procedures on the prostate gland and in the abdominal and thoracic cavities have been marred by fatal postoperative infections due to contamination of the wounds with resistant staphylococci.

A second major factor that has led to complications in patients has been the presence of antibiotic-resistant staphylococci in the nasopharynges of sick and debilitated patients who have received antibiotics for other purposes. The staphylococci, which the patients have been carrying, have been resistant to the antibiotics being administered, and this has permitted the staphylococci to reproduce rapidly with dire consequences. One of the commoner clinical entities rising from this train of events has been the appearance of a severe, and even fatal, enterocolitis, in which

‡ References 19, 38, and 84.

the patients experience a severe watery diarrhea and dehydration with shock. The contents of the stool are made up of blood, exudate, and tremendous numbers of resistant staphylococci. This complication was first pointed out by Finland,[34] and subsequent reports have accumulated in this country and abroad.§ Several antibiotics have been implicated, including penicillin, streptomycin, oxytetracycline and chlortetracycline. Many cases have occurred in patients who were treated with oxytetracycline or chlortetracycline preoperatively for purposes of reducing the bacterial population in the intestinal tract prior to surgery. Resistant staphylococci present in the intestinal tract have been allowed to propagate, while the more sensitive bacterial species have been reduced in number or killed. Some of these strains of staphylococci have produced enterotoxin, which has contributed to the diarrhea. We have recently seen a fatal case of severe enterocolitis arising in an alcoholic who had pneumococcal lobar pneumonia and was treated with penicillin, oxytetra-

TABLE 3.—*In Vitro Sensitivity of Strain of Coagulase-Positive Staphylococcus Isolated from Stool in Fatal Case of Pseudomembranous Enterocolitis Following Therapy with Erythromycin*

Antibiotic	Concentration of Antibiotic Required to Inhibit Growth, Units or γ/Ml.
Penicillin	6.3
Streptomycin	>800.0
Chlortetracycline	50.0
Oxytetracycline	100.0
Tetracycline	100.0
Chloramphenicol	50.0
Erythromycin	>200.0
Neomycin	0.38

cycline, and streptomycin. He improved considerably, but he then developed a dermatitis due to the antibiotic therapy, presumably penicillin. He was then given erythromycin, and a severe and fatal enterocolitis due to erythromycin-resistant staphylococci occurred. Autopsy revealed a severe ulceration of the entire colon, with a pseudomembranous enterocolitis. This sequence of events is of interest, since erythromycin has been advocated for the treatment of staphylococcal enterocolitis caused by the administration of the tetracycline antibiotics.[22] Table 3 shows the results of sensitivity studies carried out with the strain of Staphylococcus cultured from the stool. Other complications arising out of the use of antibiotics in patients with antibiotic-resistant staphylococci include the appearance of scarlet fever in patients receiving chlortetracycline or oxytetracycline for pertussis.[49] Pharyngeal cultures of these patients revealed the presence of a pure culture of Staphylococcus. And in other instances, when oxytetracycline was used for the treatment of chronic urinary tract infections, the predominant bacterium in the urine was the Staphylococcus.[127]

We have encountered other clinical entities due to highly resistant staphylococci. A young woman seen recently had severe ulcerating lesions of the skin, subcu-

§ References 15, 22, 33, 40, and 53 and Antibiotics, Staphylococcal Enteritis and Pseudomembranous Enterocolitis, editorial, New England J. Med. **249**:37, 1953.

TABLE 4.—*Concentrations of Antibiotic Which Failed to Inhibit Growth of Coagulase-Positive Strain of Staphylococcus Isolated from Ulcerating Lesion of Patient Shown in Figure 5*

Antibiotic	Concentration of Antibiotic That Failed to Inhibit Growth, Units or γ/Ml.
Penicillin	15.6
Chlortetracycline	31.2
Oxytetracycline	62.5
Tetracycline	31.2
Carbomycin	62.5
Erythromycin	62.5
Bacitracin	50.0
Neomycin	31.2

Fig. 5.—Severe necrosis of tissues of leg due to staphylococcal dermonecrotoxin produced by strain of Staphylococcus that was highly resistant to antibiotics. Note the surface of muscle covered by purulent exudate.

taneous tissues, and even of the underlying muscles due to a strain of Staphylococcus that not only was highly resistant to several antibiotics but that also produced dermonecrotoxin. The results of in vitro sensitivity studies carried out with this strain are presented in Table 4. Figure 5 shows a large necrotic and suppurating ulcer of the leg in this patient. This proved to be an unusual strain of Staphylococcus, since it exhibited resistance to practically all the antibiotics now available. In order that this strain would not be distributed too widely in the hospital, this patient was kept in strict isolation for several weeks. She recovered after the use of large quantities of parenteral penicillin. The results of sensitivity studies on a strain of coagulase-positive Staphylococcus isolated from a brain abscess in another patient are shown in Table 5. It is to be noted that the organisms were particularly sensitive to bacitracin and to neomycin and that they were sensitive to chloramphenicol.

Finally, the Staphylococcus is a not infrequent cause of pneumonia. Staphylococcal pneumonia is a serious complication of influenza.[36] An increasing number of cases of severe respiratory disease due to antibiotic-resistant staphylococci is being encountered in debilitated or elderly patients.

TREATMENT OF STAPHYLOCOCCAL INFECTIONS

With recognition that staphylococcal infections vary from a mild furunculosis or impetigo to a severe and fulminating septicemia, this discussion is concerned primarily with the more serious forms of sepsis. However, control and eradication of a relatively benign local lesion may prevent a more serious systemic infection. The immediate objective of the physician in dealing with an uncomplicated mild pyoderma or other localized lesion is to maintain the blood stream free of bacteria. This cannot be achieved by merely applying an antibiotic or combination of anti-

TABLE 5.—*Concentrations of Antibiotics Required to Inhibit Growth of Strain of Staphylococcus Isolated from a Brain Abscess*

Antibiotic	Inhibiting Concentration of Antibiotic, Units or γ/Ml.
Penicillin	800
Streptomycin	>2500
Chlortetracycline	400
Oxytetracycline	200
Tetracycline	100
Chloramphenicol	12.5
Erythromycin	400
Carbomycin	200
Bacitracin	3.1
Neomycin	0.25

biotics to the local lesion. In many instances it is prudent to combine local therapy with drainage of the lesion and with the oral or parenteral administration of antibiotics. For local use we have found bacitracin or neomycin, or a combination of the two antibiotics, to be highly effective.

In managing the severer forms of staphylococcal sepsis several procedures should be followed. First, before any chemotherapeutic agent is administered, the offending micro-organisms should be isolated and identified. Second, all suppurating and necrotic tissues and cavities should be drained surgically. Third, treatment with an antibiotic, preferably with a combination of antibiotics, should be instituted as soon as possible, and the antibiotics should be selected on the basis of clinical experience which at the time has demonstrated those agents to be most effective against a majority of the strains. In the meantime, in vitro tests should be carried out to determine the sensitivity of the culture to a number of antibiotics. Fourth, in utilizing antibiotics for staphylococcal sepsis one must be as aggressive and as persistent as one is in the therapy of subacute bacterial endocarditis due to alpha hemolytic streptococci. Treatment should not be discontinued too soon, since severe, and even fatal, relapses may occur in patients who have manifested marked improvement. These principles are in accord with the sensible and practical recommendations of Howe.[52]

We now employ a combination of antibiotics in the treatment of cases of severe staphylococcal sepsis, particularly in patients with septicemia. Such combinations can have an additive or synergistic action against staphylococci, and the presence of two antibiotics may decrease the possibility of the appearance of resistant microorganisms, such as can occur when only one agent is used. Some investigators || have pointed out on the basis of in vitro experiments that some combinations of antibiotics may actually kill fewer bacteria than does either one of the antibiotics in the combination. There is no doubt that such antagonism does occur under experimental conditions, but I have never encountered any convincing evidence in human patients that antagonism has taken place with any infections in which several combinations of antibiotics have been used. On the other hand, there is general agreement that combinations are highly effective in the treatment of such diseases as tuberculosis, brucellosis, and subacute bacterial endocarditis.

Penicillin is still the most effective and most desirable agent for the treatment of staphylococcal sepsis, if the causative strain is sensitive to the in vitro action of the antibiotic. But, knowing that approximately 60% of the strains isolated from our clinical material are highly resistant to penicillin, we do not initiate treatment with penicillin alone. Time is precious in the treatment of a desperately ill patient, and, while awaiting the results of in vitro tests, we start intensive treatment with a combination of drugs. Crystalline penicillin G in aqueous suspension is given intramuscularly in a dose of 500,000 units every four hours. For the first 48 to 72 hours, an additional 500,000 units are administered intravenously in 10 ml. of saline solution every 12 hours. Plastic tubing for continuous intravenous infusions is not used because of the threat of local thrombophlebitis. If the patient has good renal function, bacitracin is given along with the penicillin.¶ Bacitracin is an excellent antistaphylococcal agent, but it is nephrotoxic. However, we have encountered no serious renal disturbances in patients receiving not more than 80,000 units daily. We administer 20,000 units intramuscularly every six hours. If the patient has seriously impaired renal function, erythromycin has been used with penicillin in a total daily dose of 2 to 3 gm. With the foregoing antibiotic therapy and supportive treatment under way, attention is then turned to the results of in vitro sensitivity tests. The disc method (Difco) provides a simple and rapid procedure for such tests, though we have found in comparative tests that the tube-dilution method provides a more precise end point.[119] To determine whether a strain produces penicillinase, the procedure of Haight and Finland [45] is followed.

If the in vitro test reveals that the strain is sensitive to the action of penicillin in low concentrations, treatment with penicillin and bacitracin is continued for several days and, if the condition of the patient demands it, up to two to four weeks. If the strain proves to be highly resistant to penicillin, then penicillin is discontinued and therapy with bacitracin is continued along with erythromycin or, possibly, chloramphenicol. Recent studies suggest that bacitracin and chloramphenicol are an effective combination.[89]

The clinician really encounters serious trouble if the causative strain is resistant to penicillin and at the same time the patient has a marked reduction in renal function. This is not an infrequent occurrence. Under these circumstances, we still

|| References 54 and 58.

¶ References 75 and 76.

adhere to the use of a combination of drugs, such as erythromycin and chloramphenicol, or chloramphenicol and tetracycline, in an attempt to control a desperate clinical situation. Except in extreme and rare cases, we have abandoned the parenteral use of neomycin as recommended by some for staphylococcal endocarditis.[90] We had previously found neomycin to be highly nephrotoxic and ototoxic when given parenterally.[120] Recently, neomycin was given to a patient seriously ill with staphylococcal endocarditis. The patient became deaf after receiving 1 gm. of neomycin daily for two weeks, and he finally died. Streptomycin or dihydrostreptomycin is not used with penicillin unless a penicillin-sensitive strain is isolated. Under these circumstances 0.5 gm. of equal parts of streptomycin and dihydrostreptomycin is administered intramuscularly every 8 to 12 hours. Streptomycin is not used if the strain is highly resistant to penicillin, since most of these strains have been found to be highly resistant to streptomycin as well.

Too much stress cannot be placed upon the importance of eliminating all foci of suppuration. Exudative effusions of the serous cavities, such as the pleural

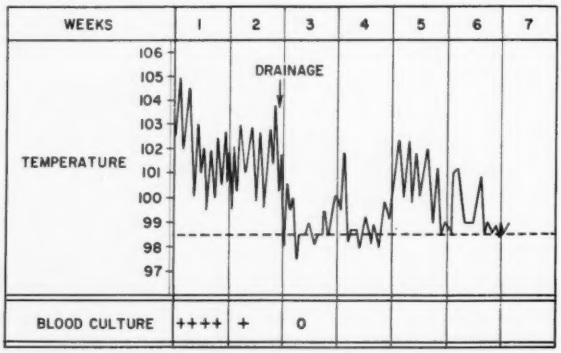

Fig. 6.—Prompt decline in fever and eradication of bacteremia following surgical drainage of staphylococcal osteomyelitis in preantibiotic period.

pericardial, and synovial spaces, should be drained, and solutions of penicillin or bacitracin should be introduced. It may be desirable to tie off thrombophlebitic vessels. Prior to the present antibiotic era, the therapeutic advantage of draining suppurating foci was well known. Figure 6 illustrates the course of a patient with staphylococcal sepsis and persistent bacteremia who improved dramatically following the surgical drainage of osteomyelitis of a long bone.

A dramatic therapeutic response was observed recently, illustrating the value of selecting the proper combination of antibiotics for a severe case of staphylococcal sepsis. The clinical course of this patient is shown in Figure 7. She was a 78-year-old woman who had influenza followed by multiple pulmonary abscesses due to coagulase-positive staphylococci. In addition, the presence of staphylococcal bacteremia was established. She was moribund upon entry into the hospital, and her condition appeared hopeless. Therapy was initiated with a combination of penicillin and oxytetracycline. Little improvement occurred. It is to be noted in the Figure that the strain of Staphylococcus isolated from this patient was highly resistant

in vitro to the two drugs which she was receiving. Possessed with this knowledge, the clinicians administered bacitracin and erythromycin, and prompt recovery ensued.

It should be emphasized that staphylococcal bacteremia would still be a very serious disease even if antibiotic-resistant staphylococci had not appeared as a further complication. Fatal cases of staphylococcal sepsis are still being encountered in which the causative bacteria are not resistant and in which properly selected antibiotics have been administered. Delay in starting treatment and the attitude of taking the initial phases of the illness too lightly have been additional deterrents to recovery in the patients.

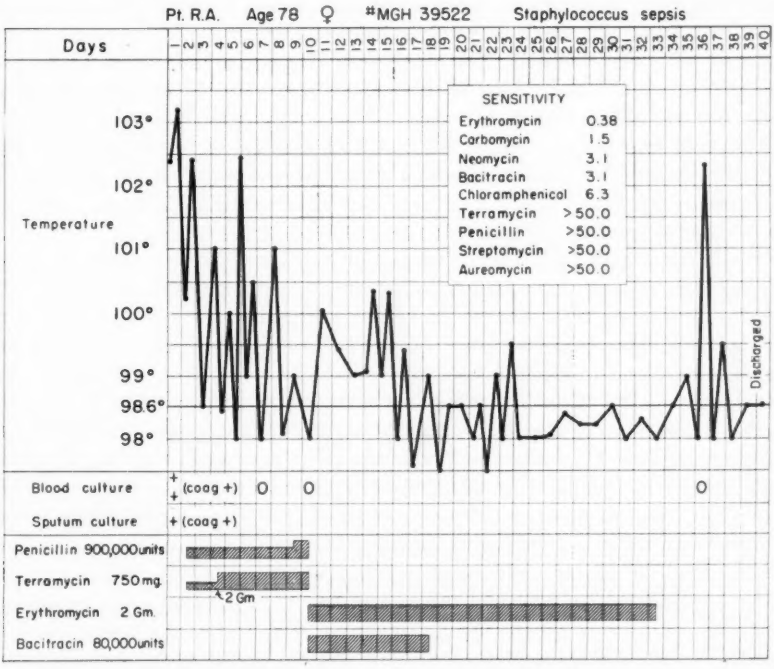

Fig. 7.—Clinical course of staphylococcal pneumonia following influenza in aged patient. Note initial treatment with improperly selected antibiotic. Prompt response to combination of bacitracin and erythromycin.

The story of antibiotic therapy over a decade in the management of staphylococcal diseases has been that of the appearance of resistant strains as each antibiotic is introduced and widely used. Little hope for circumventing this sequence resides in treating patients with combinations of drugs or in strictly isolating patients with staphylococcal sepsis undergoing treatment. The problem arises out of the widespread use of an antibiotic among the public at large so that members of a healthy population soon act as carriers of resistant staphylococci, which have been selected out by the antibiotic. Fortunately, of all bacterial species, the Staphylococcus constitutes the only serious and continuing menace to human health because of this factor of resistance appearing with successive antibiotics. For the present,

patients with staphylococcal sepsis should be treated with combinations of antibiotics carefully chosen on the basis of dependable in vitro sensitivity tests. Continued research should be aimed at acquiring agents that are nontoxic for the host and effective against the staphylococci and that overcome the problem of resistance. Since penicillin is such an effective agent in those instances in which the organisms are sensitive and since penicillin resistance is correlated with the production of the enzyme penicillinase, efforts should be aimed at inactivating this enzyme in the body. This problem may not be insurmountable.

SOME CONCLUDING COMMENTS

One of the greatest advancements in medical practice in the last decade has been the introduction of the antibiotics. The impact of these agents upon the course of many infections has been so remarkable that some diseases have been almost eliminated as serious entities. But along with this benefit to human health have come problems, and not the least of these is the appearance of strains of Staphylococcus that are resistant to the destructive action of the antibiotics. Physicians who have entered into practice within the last decade might be moved to look upon antibiotic resistance as something new, a heretofore unrecognized threat to successful chemotherapy. But, as with so many discoveries in medical science, our predecessors had an uncanny insight into this biological phenomenon.

If one turns back to the series of papers by Erlich,[32] which appeared almost 50 years ago, one can read an exposition on chemotherapy and the problems of microbial resistance that read as though these papers were prepared after the more modern experience with the antibiotics. A particularly penetrating and provocative report was made by Browning,[16] in 1907, who was one of Erlich's pupils at Frankfort on the Main. Browning had worked with trypanosomiasis in experimentally infected mice and had evaluated several chemicals as prophylactic and therapeutic agents. He found that his strain of trypanosome, the Naguna strain, was a highly lethal parasite for mice, but he could protect his mice with trypan-red, trypan-blue, and parafuchsin. He also observed that this strain could become resistant to all three of these agents. Furthermore, even in those instances in which resistance did not appear, a chronic infection might ensue instead of a fatal disease, and so he cogitated on ways and means not only of preventing the appearance of resistance but also of eliminating the infection. Out of his experiments and his thoughts he recorded some principles of therapy for human beings that are just as applicable today with our more modern agents as they were a half century ago. He emphasized that resistance of the organisms was a permanent characteristic of the invading parasites. As aids in the prevention of chronicity of the infection and of protection against the appearance of resistant parasites, he suggested just what we have advocated for the treatment of staphylococcal sepsis, namely, energetic and aggressive treatment with a combination of drugs that had been selected on the basis of sensitivity tests carried out in the laboratory.

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EVALUATION OF PROVOCATIVE BLOOD ENZYME TESTS EMPLOYED IN DIAGNOSIS OF PANCREATIC DISEASE

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THE DIAGNOSIS of diseases of the pancreas has at all times presented a challenging problem to the clinician. The ability to detect signs of functional abnormality of this organ is limited by the fact that the pancreas has a large functional reserve and has the capacity for rapid return to normal activity.* Despite extensive destruction of the gland, few clinical signs may be present. Then, too, the anatomical location of the gland renders it inaccessible to the usual methods of physical diagnosis. Although great advances have been made in the roentgenographic approach to the pancreas, no reliable radiographic methods have, as yet, been developed to visualize it other than by its relations to neighboring viscera. The clinician, therefore, in diagnosing pancreatic disease, is dependent for all practical purposes upon three types of laboratory procedures:

1. study of the duodenal contents
2. study of the blood enzyme levels
3. study of blood coagulation factors

Duodenal drainage following various pancreatic stimuli has proved a most valuable aid in pancreatic diagnosis.† The test procedure, unfortunately, requires extremely careful technique, is time-consuming, and is not the most pleasant type of test from the point of view of the patient. An uncooperative subject defies duodenal intubation. These obstacles, coupled with the periodic difficulty in obtaining secretin, have deterred some clinics from setting up the secretin test procedure, despite its diagnostic value.

Tests based upon the effect of pancreatic disease on blood coagulation factors [9] represent a relatively recent approach to the problem. Innerfield and his associates introduced the antithrombin titer index, a test deriving from the observation of altered levels of anticoagulant factors in the blood in pancreatic disease. These are theoretically the result of elevated blood trypsin concentrations.‡ Elevated titers have been reported in patients with acute pancreatitis even after the blood amylase

The secretin used in this study was supplied by Eli Lilly & Company.

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* References 1 and 2.

† References 1-8.

‡ References 10 and 11.

has returned to normal.§ Elevated titers also have been observed in pancreatic cysts,[13] pancreatic cancers,[14] and in some cases of chronic pancreatitis [15]; in cystic fibrosis of the pancreas, low antithrombin titers occasionally have been seen.[16] Shingleton, Anlyan, and Hart, working along lines similar to those of the Innerfield group, have developed the paritol blood-coagulation test for pancreatic diagnosis.[17] By use of this sensitized blood-clotting procedure before and after administration of a pancreatic stimulant, a change in blood coagulability was found in a significant number of patients with chronic relapsing pancreatitis and with pancreatic cancer.

The contributions of the Innerfield and Shingleton groups are interesting and provocative. Much works remains to be done before the significance and reliability of their procedures in the diagnosis of pancreatic disease are confirmed and established. Their original approaches should do much to open new avenues of research in problems of etiology, diagnosis, and treatment of pancreatic disease.

The most commonly used laboratory procedures employed in the diagnosis of pancreatic disease are those involving study of the concentration of blood enzymes. Serum amylase is the most easily measured enzyme. Its introduction as a diagnostic aid is the result of the classic investigations of Elman.|| The work of Wohlgemuth,[20] Somogyi,¶ and others # has helped to simplify and extend its utilization.

Serum amylase is derived from the pancreas, the salivary glands, the liver, and possibly other organs. The amylase level is almost always elevated at some stage in the course of acute pancreatitis, values above 200 mg. per 100 cc. (Somogyi) being accepted in most laboratories as pathognomonic of the disease. The increase in circulating enzyme is assumed by Howard, Smith, and Peters [27] to be due to back-pressure within the pancreatic duct system with retrograde passage of the enzyme through the capillaries into the blood stream. This "spill-over" theory has been extended by Janowitz and Hollander,[28] who suggest that enzymes are normally secreted not only into the gland lumina (exocrine) but also into the blood stream by way of the tissue spaces (endocrine). In acute pancreatitis the increased blood amylase may be, then, an illustration of the effect of the disease on the "physiological partition." [28]

That elevation of the blood amylase occurs at some point early in the course of acute pancreatitis is, by now, a well-established fact, though minimal elevations cannot be accepted as absolute proof of acute pancreatitis. Increased blood amylase values have been reported in patients with perforated peptic ulcers,* intestinal obstruction,[30] and uremia [31]; after cholangiography [32]; in biliary tract disease, especially choledocholithiasis,[33] and, what is most disquieting, after codeine or morphine injection.[33] The rise in blood amylase in acute pancreatitis persists, usually, for a few hours, rarely for more than 72 hours, making it imperative to do amylase determinations early and frequently in the course of the disease. A normal blood amylase level need not exclude acute pancreatitis.

This disadvantage of the blood amylase determination has been overcome by some by the utilization of the serum lipase value.† Serum lipase parallels serum

§ References 11 and 12.
|| References 18 and 19.
¶ References 21-24.
# References 25 and 26.
* References 29 and 30.
† References 34-38.

amylase. Elevated lipase levels may persist in acute pancreatitis and even in pancreatic carcinoma after the amylase has returned to normal levels.[35] Unfortunately, lipase determinations are not done in most laboratories, because of the complexity of the procedure, the length of analysis time, and the difficulty in defining the physical conditions of incubation.

Other investigators have attempted to diagnose acute pancreatitis in the later phases or in patients with normal blood amylase by studying the urinary amylase. Amylase is excreted by the kidney as a threshold substance. When the blood amylase is high, there is a great increase in the urinary amylase unless there is concomitant renal insufficiency.‡ The urinary amylase thus tends to parallel the blood concentration, with the exception that extremely wide variations occur normally with changes in urinary specific gravity. Dozzi [40] has reported cases of acute pancreatitis which showed elevation of the urinary amylase while the blood amylase was normal. The experience of most clinics with urinary amylase determination, however, has not been encouraging.

While unanimity of opinion exists as regards the value of blood serum enzyme determinations in acute pancreatitis, no such agreement attends the worth of these enzyme levels in chronic pancreatic disease, such as pancreatitis and carcinoma.§ In chronic pancreatic disease elevations of blood amylase and lipase are assumed to be the result of obstruction to the flow of pancreatic juice through a ductal system which may be compressed by fibrotic tissue around it, by calculi both within and around the ducts, and by cells obtunding the ducts, as in cancer. Johnson and Bockus [37] have reported hyperlipasemia in two-thirds of a series of cases of pancreatic cancer. Gambill, Waugh, and Dockerty [42] have reported a case of pancreatic carcinoma in which both the serum amylase and lipase were elevated persistently for a period of one year. These observers emphasized that such persistent elevations of pancreatic blood enzymes may be characteristic of pancreatic tumor. However, in most cases of chronic pancreatitis and pancreatic cancer, fasting blood enzyme levels contribute little to the diagnosis.[41]

Attempts to overcome the deficiencies of blood enzyme determinations in the diagnosis of acute pancreatitis and to extend the scope of these diagnostic laboratory procedures to include chronic pancreatic disease and pancreatic tumors have resulted in the provocative blood enzyme tests. In these, the level of the blood enzymes is studied at intervals for several hours before and after the administration of drugs, either singly or in combinations, designed to produce one or more of the following effects on the pancreas: (1) stimulation of the flow of pancreatic juice (secretin), (2) stimulation of the production of pancreatic enzymes (methacholine [Mecholyl], bethanechol [Urecholine]), and/or (3) blocking of the outflow tract of the pancreatic duct system (morphine). The responses are interpreted according to the drugs used and the alteration of the enzyme levels during the procedure.

The theoretical concepts upon which the provocative enzyme tests were conceived are rooted in the basic physiology of the external pancreatic secretion. Achard and Clerc,[43] in 1901, found that injection of pilocarpine caused an elevation of the serum amylase of rabbits. Their findings were confirmed by Lœper and Ficaï.[44] Antopol, Schiffrin, and Tuchman,[45] in 1934, found that methacholine

‡ References 31 and 39.

§ References 37, 38, and 41.

(acetyl-β-methylcholine), with or without physostigmine (eserine), increased the blood amylase level. Similar results were obtained in normal dogs by Guelzow [46] with pilocarpine and acetylcholine and by Popper, Olson, and Necheles,[47] using methacholine and physostigmine. The latter investigators also reported an elevation of the blood lipase following administration of these drugs whenever the pancreatic duct was ligated. They extended their studies to note that, while methacholine and secretin produced an elevation in blood lipase in the intact dog, no such rise was seen when there was pancreatic fibrosis or atrophy.[48] Other physiological studies along these lines include the investigations of Kumagai and Osato,[49] Friedman and Thompson,[50] and Popper and Plotke.[51] These investigators showed that parasympatheticomimetic drugs (methacholine with or without physostigmine or neostigmine [Prostigmine]) could cause elevations of the blood amylase and lipase and that these elevations were vitiated by previous pancreatectomy or pancreatic duct ligation.

The first efforts to utilize the alteration of blood enzyme levels in response to pancreatic stimulants as a diagnostic procedure were made by Ferrando and by Lagerlöf. Ferrando,[52] studying the blood lipase curves after carbaminocholine (Doryl) administration, observed transient elevations in normal subjects which were not obtained in patients with pancreatitis. Lagerlöf,[53] using secretin to stimulate pancreatic flow and morphine to cause spasm of the sphincter of Oddi, thereby producing obstruction to pancreatic flow, introduced the "second secretin test." This procedure occasionally caused pain suggestive of biliary colic. Many of the patients showed elevation of the serum amylase level.

These preliminary reports of Ferrando and of Lagerlöf offered a very simple and promising means of diagnosing pancreatic disease. There followed many studies based upon their physiological concepts and designed to define the responses to be expected in normal patients and in persons with pancreatic disease.

Myhre, Nesbitt, and Hurley,[54] using a combination of morphine and secretin, obtained a rise in serum enzymes in normal persons, whereas the same procedure produced no rise in patients suffering from pancreatitis. Snape, Wirts, and Friedman [55] found elevations of blood enzymes in normal patients following administration of secretin and morphine. Later, Wirts and Snape,[8] working with methacholine, bethanechol, and bethanechol combined with morphine, obtained enzyme elevations in normal patients with all three medications, whereas in patients with pancreatitis bethanechol produced enzyme increases only in those instances in which there was pancreatic duct obstruction.

Lopusniak and Bockus [56] used secretin only in normal patients and in subjects with advanced pancreatic insufficiency. No appreciable rise in serum enzymes was observed. However, marked elevations followed secretin administration in patients with elevated fasting serum enzymes and in those with pancreatic duct obstruction due to cancer. Knight, Muether, and Sommer [57] found a rise in serum enzymes in their cases of chronic recurrent pancreatitis following stimulation with neostigmine.

Sachar, Probstein, and Whittico [58] and Burke, Plummer, and Bradford [59] conducted extensive studies of the serum enzyme responses to drugs. Sachar and co-workers worked with combinations of secretin, neostigmine, morphine, and methacholine. Methacholine and secretin following morphine were the most effective stimulus, but even this combination did not uniformly produce a rise in normal persons. Nor were these authors successful in obtaining elevations in patients with

cancer, recent acute pancreatitis, or calcification of the pancreas. The Burke group found elevated values after morphine, methacholine, and secretin in a significant number of normal patients and a much less constant and less marked response in patients with known pancreatic disease.

Heffernon and Gunter,[60] with secretin and methacholine, found no elevation in 15 normal patients, whereas there was a significant rise in 3 out of 14 patients with proved pancreatic disease. Sanchez-Ubeda and Rousselot,[61] with secretin and methacholine, observed frequent elevations in patients with and without pancreatic disease. A statistical study of their results with serum amylase indicated that the

TABLE 1.—*Summary of Serum Enzyme Responses to Pancreatic Secretagogues as Reported in Previous Investigations*

Observer	Drug Used as Stimulant	Serum Enzyme Responses *	
		Normal Patients	Patients with Pancreas Disorders
Ferrando [52]	Carbaminocholine	+ (Lipase)	— (Lipase)
Lagerlöf [53]	Secretin, morphine	+ (Amylase) †	— (Amylase) †
Myhre, Nesbitt, & Hurley [54]	Secretin	—	—
	Secretin, morphine	+	—
	Secretin, morphine, methacholine	+	—
Snape, Wirts, & Friedman [55]	Secretin, morphine	+	..
Wirts & Snape [8]	Methacholine	+	..
	Bethanechol	+	± ‡
	Bethanechol, morphine	+	..
Lopusniak & Bockus [56]	Secretin	—	± §
Knight, Muether, & Sommer [57]	Neostigmine	..	+
Sachar, Probstein, & Whittico [58]	Secretin	—	..
	Methacholine	—	..
	Neostigmine	—	—
	Neostigmine, morphine	±	—
	Secretin, methacholine, morphine	±	..
Burke, Plummer, & Bradford [59]	Secretin, methacholine	—	..
	Secretin, methacholine, morphine	+	±
Heffernon & Gunter [60]	Secretin	—	±
	Secretin, methacholine	—	..
Sanchez-Ubeda & Rousselot [61]	Secretin, methacholine	±	± ‖
Malinowski [62]	Neostigmine	± (Amylase)	± ¶
Royer, Noir, & Fernández Darío [41]	Carbaminocholine	±	..
	Morphine, carbaminocholine	±	..
	Secretin	± (Amylase)	— (Lipase)
	Methacholine	± (Amylase)	— (Lipase)

* Unless stated otherwise both lipase and amylase were studied; +, elevation; —, no elevation; ±, variable.
† Response sometimes associated with abdominal pain.
‡ Elevations with patients with pancreatic duct obstruction, otherwise no elevations.
§ Elevations in pancreatic duct obstructions or if fasting serum enzyme level already elevated; in advanced pancreatic disease, no elevations.
‖ Statistically lesser elevations observed in disease group.
¶ Minimal elevations in pancreatic disease without pancreatic duct obstruction; more marked elevations in patients with pancreatic disease and pancreatic duct obstruction.

degree of response was greater in the disease group. No such pattern was discerned for serum lipase. Royer, Noir, and Fernández Darío [41] studied the blood amylase and lipase curves after administration of carbaminocholine, carbaminocholine and morphine, secretin, and methacholine. They noted variable responses in individual cases and in the entire group. Elevations of amylase were encountered with greater regularity than elevations of lipase.

It is apparent from the above review of the literature, which is summarized in Table 1, that the extensive investigations by many groups into the serum pancreatic

enzyme response to various secretagogues have produced such disparate findings and conclusions as to result in considerable confusion. The present communication is the report of an investigation undertaken to confirm or at least to clarify the significance of provocative enzyme tests as diagnostic procedures in pancreatic disease.

METHODS AND MATERIAL

The patients studied were from the ward and private services of the Mount Sinai Hospital, New York. The diagnostic investigations were conducted by physicians not associated with the research problem. The subjects chosen were in two groups: (1) those without evidence of pancreatic disease and (2) those with proved pancreatic disorder. The diagnosis of acute pancreatitis was made on the basis of either operation or the demonstration of an elevated blood amylase. The diagnosis of chronic pancreatitis depended upon exploration or the finding by x-ray of pancreatic calcification. All the patients with pancreatic cancers were operated upon.

The drugs employed in this study were secretin, morphine, methacholine, and bethanechol, either used singly or in combinations. Secretin was administered intravenously in 100 clinical unit dosage. Morphine was given to patients subcutaneously in 15 mg. doses. The stimulating dose of methacholine was 20 mg. subcutaneously and that of bethanechol 5 mg. subcutaneously.

The patients were studied according to the following protocol. A fasting blood sample was obtained. Then, the drug or drug combination employed was administered. After this, blood specimens were drawn at one-half hour, one hour, one and one-half hours, two hours, three hours, and four hours. As the study progressed, it was found expedient to eliminate the half-hour, one-and-one-half-hour, and four-hour samples. This simplified the investigation but did not alter the significance of the data obtained in response to the various drug combinations.

The amylase determinations were done by a modified Somogyi starch-hydrolysis technique. The sugar values were obtained either by Shaeffer-Hartman titration or by photoelectric colorimetry. All analyses were performed in duplicate. In some instances, more than one study was done on the same patient.

The normal range of amylase values in this laboratory with the method used is from 50 to 200 mg. per 100 cc. Values below 50 mg. are frequently observed in normal patients and are not considered abnormal.

RESULTS

The results of this investigation are given in Table 2. In all, 192 studies were performed. The data are listed according to the drug and the drug combinations, with the control groups separated from the groups of patients with proved pancreatic disease.

Secretin.—Secretin alone caused no rise of blood amylase in 18 patients without pancreatic disease. Of 15 patients with proved pancreatic disease, only 1 patient exhibited a rise in blood amylase following the drug. This rise was small, from a level of 74 to 114 mg. per 100 cc. at three hours.

Morphine.—After morphine, the blood amylase was found to rise in 2 out of 13 control patients. In these two patients, the elevations were definite, from 72 to 206 mg. per 100 cc. in one instance and from 65 to 180 mg. in the other case. Of the 10 patients with pancreatic disease, elevated blood amylase curves were observed in 2. One patient with acute pancreatitis showed a rise from 126 to 198 mg. per 100 cc. The other subject, with acute and chronic pancreatitis, exhibited a rise from 284 to 368 mg. per 100 cc.

Methacholine.—Methacholine, when administered to a control group of 16 patients, evoked amylase elevations in 4 patients. The rises seen were, respectively, from 85 to 157 mg., from 73 to 190 mg., from 90 to 196 mg., and from 123 to 201 mg., per 100 cc. Of 15 patients with pancreatic disorders, methacholine caused

TABLE 2.—*Serum Amylase Response Data After Various Pancreatic Secretagogues in Patients With and Without Pancreatic Disease*

Drug	Diagnosis	Serum Amylase Response to Drug, Mg./100 Cc. Glucose			
		Control	1 Hr.	2 Hr.	3 Hr.
Secretin	A. Patients without pancreatic disease				
	1. Virus pneumonia	178	150	146	138
	2. Incision and drainage carbuncle	167	142	148	141
	3. Duodenal ulcer	48	47	52	56
	4. Resection thyroglossal cyst	142	121	128	134
	5. After appendectomy	49	44	56	56
	6. Saphenous vein ligation	92	84	88	88
	7. Regional ileitis	37	44	46	42
	8. Diabetes mellitus	76	82	80	80
	9. Gastric ulcer	200	186	196	192
	10. Postcholecystectomy syndrome	66	70	72	74
	11. Diffuse jejunoileitis	45	48	48	45
	12. Postcholecystectomy syndrome	121	118	128	128
	13. After appendectomy	135	151	149	147
	14. After inguinal hernioplasty	98	88	90	96
	15. Acute hepatitis	40	40	44	46
	16. Chronic ulcerative colitis	51	52	58	52
	17. Diverticulitis colon	39	34	42	40
	18. Postcholecystectomy syndrome	96	98	94	98
	Average, 18 cases	93	89	93	92
	B. Patients with pancreatic disease				
	1. Acute pancreatitis	156	179	196	196
	2. Chronic pancreatitis	42	48	56	94
	3. Acute pancreatitis	198	192	196	176
	4. Carcinoma head pancreas	49	53	50	55
	5. Acute pancreatitis	120	90	94	96
	6. Carcinoma head pancreas	74	94	110	114
	7. Acute pancreatitis	58	60	68	60
	8. Incision and drainage pancreatic abscess	46	48	52	50
	9. Carcinoma head pancreas	38	27	34	34
	10. Acute pancreatitis	125	135	137	130
	11. Chronic pancreatitis, pancreatic calcinosis	82	78	78	79
	12. Carcinoma head pancreas	72	86	78	78
	13. Chronic pancreatitis	86	78	82	80
	14. Carcinoma body pancreas	88	96	88	92
	15. Carcinoma head pancreas	130	124	124	140
	Average, 15 cases	91	92	96	98
Morphine	A. Patients without pancreatic disease				
	1. Chronic cholecystitis	94	92	88	84
	2. Postcholecystectomy syndrome	88	84	64	64
	3. Psychoneurosis	58	56	54	66
	4. After repair incisional hernia	66	68	60	56
	5. Regional ileitis	72	134	168	206
	6. Sprue	116	108	122	114
	7. Chronic cholecystitis	134	112	118	112
	8. Chronic ulcerative colitis	65	180	160	118
	9. Postcholecystectomy syndrome	47	49	45	45
	10. Diabetes mellitus	84	88	90	95
	11. After inguinal hernioplasty	154	135	137	152
	12. Pernicious anemia	76	76	78	78
	13. Bronchiectasis	145	140	148	140
	Average, 13 cases	92	102	103	103
	B. Patients with pancreatic disease				
	1. Acute pancreatitis	126	112	108	198
	2. Pancreatic calcinosis	34	38	25	38
	3. Carcinoma head pancreas	76	84	72	70
	4. Carcinoma head pancreas	118	87	92	96
	5. Acute pancreatitis	96	94	94	92
	6. Chronic relapsing pancreatitis	56	50	58	52
	7. Carcinoma body pancreas	78	76	76	74
	8. Chronic pancreatitis, pancreatic cyst	163	168	167	172
	9. Chronic pancreatitis	66	62	72	65
	10. Acute and chronic pancreatitis	294	330	352	368
	Average, 10 cases	90	110	113	123

TABLE 2.—*Serum Amylase Response Data After Various Pancreatic Secretagogues in Patients With and Without Pancreatic Disease*—Continued

Drug		Diagnosis	Serum Amylase Response to Drug, Mg./100 Cc. Glucose: Control	1 Hr.	2 Hr.	3 Hr.
Bethanechol	A.	Patients without pancreatic disease				
		1. Chronic cholecystitis	94	95	90	83
		2. Sprue	82	86	88	96
		3. Psychoneurosis	62	50	46	48
		4. Functional gastrointestinal complaints	64	68	74	64
		5. Essential hypertension	62	68	90	72
		6. Diffuse jejunoileitis	114	110	116	116
		7. Diabetes mellitus	75	77	77	79
		8. Chronic cholecystitis	138	142	132	148
		9. After appendectomy	58	72	78	96
		10. Hiatus hernia	94	90	102	112
		11. After hemorrhoidectomy	76	96	116	114
		12. Pernicious anemia	86	102	116	126
		Average, 12 cases	84	88	94	96
	B.	Patients with pancreatic disease				
		1. Chronic relapsing pancreatitis	48	52	50	56
		2. Acute pancreatitis	178	206	246	224
		3. Chronic pancreatitis	46	48	40	38
		4. Carcinoma body pancreas	24	30	34	26
		5. Chronic pancreatitis, cystoenterostomy	65	78	96	138
		6. Carcinoma head and body pancreas	89	86	84	78
		7. Carcinoma head pancreas	96	98	92	102
		8. Acute pancreatitis	134	142	137	139
		9. Pancreatic calcinosis	74	71	71	79
		10. Chronic pancreatitis, cyst head pancreas	125	141	148	161
		Average, 10 cases	88	95	100	104
Methacholine	A.	Patients without pancreatic disease				
		1. After appendectomy	32	31	29	34
		2. Pernicious anemia	53	57	71	65
		3. After appendectomy	140	139	139	141
		4. Fibroid uterus	123	178	201	196
		5. Regional ileitis	50	48	48	47
		6. Chronic thyroiditis	88	94	96	92
		7. After inguinal hernioplasty	84	85	92	87
		8. Chronic cystic mastitis	90	190	196	195
		9. Neurofibroma	73	74	71	74
		10. Chronic cholecystitis	30	30	31	80
		11. Fibrosarcoma	117	123	118	118
		12. Diffuse jejunoileitis	34	36	36	32
		13. Postcholecystectomy syndrome	118	120	120	133
		14. Diffuse jejunoileitis	30	30	41	41
		15. Cirrhosis	85	117	136	157
		16. Chronic cholecystitis	73	118	140	190
		Average, 16 cases	79	91	98	105
	B.	Patients with pancreatic disease				
		1. Acute pancreatitis	68	66	66	66
		2. Carcinoma head pancreas	115	206	192	205
		3. Chronic pancreatitis	39	45	76	88
		4. Carcinoma pancreas	17	51	51	31
		5. Acute pancreatitis	76	83	88	95
		6. Chronic pancreatitis	82	83	78	78
		7. Pancreatic calcinosis	78	74	74	74
		8. Incision and drainage pancreatic abscess	78	85	78	76
		9. Acute pancreatitis	136	184	284	266
		10. Carcinoma head pancreas	94	72	102	78
		11. Carcinoma head pancreas	154	150	136	146
		12. Chronic relapsing pancreatitis	47	74	96	164
		13. Acute and chronic pancreatitis	91	97	96	96
		14. Subacute pancreatitis	184	206	275	315
		15. Carcinoma body pancreas	65	68	70	89
		Average, 15 cases	88	104	117	95

TABLE 2.—*Serum Amylase Response Data After Various Pancreatic Secretagogues in Patients With and Without Pancreatic Disease*—Continued

Drug	Diagnosis	Serum Amylase Response to Drug, Mg./100 Cc. Glucose			
		Control	1 Hr.	2 Hr.	3 Hr.
Secretin & Morphine	A. Patients without pancreatic disease				
	1. Diaphragmatic hernia	28	32	34	31
	2. Acute hepatitis	53	114	98	90
	3. Gastric ulcer	38	40	36	36
	4. After appendectomy	180	170	168	166
	5. After inguinal hernioplasty	132	83	88	89
	6. Arteriosclerotic heart disease	34	32	38	37
	7. Virus pneumonia	64	72	68	70
	8. After appendectomy	31	31	32	37
	9. Postcholecystectomy syndrome	124	125	135	133
	10. After inguinal hernioplasty	94	87	85	83
	11. Cirrhosis	47	55	52	52
	12. Postcholecystectomy syndrome	45	53	52	53
	13. Chronic duodenal ulcer	95	96	96	96
	14. After sympathectomy for hypertension	117	100	98	113
	15. Choledocholithiasis	68	72	84	96
	16. After resection papilloma breast	72	96	113	97
	17. Pernicious anemia	58	72	52	76
	Average, 17 cases	75	78	78	84
	B. Patients with pancreatic disease				
	1. Acute pancreatitis	90	91	86	93
	2. Chronic pancreatitis	63	62	66	66
	3. Carcinoma head pancreas	50	46	46	47
	4. Carcinoma head pancreas	162	148	155	154
	5. Acute pancreatitis	60	60	63	63
	6. Chronic pancreatitis	76	82	82	86
	7. Chronic pancreatitis, calcinosis	78	158	212	216
	8. Chronic pancreatitis, postcholecystectomy syndrome	34	32	38	28
	9. Acute pancreatitis	132	146	164	214
	10. Inision and drainage pancreatic abscess	182	216	312	202
	11. Pancreatic calcinosis	84	84	76	72
	12. Carcinoma body pancreas	114	118	125	135
	13. Adenomatosis pancreas	56	50	62	55
	Average, 13 cases	91	99	114	110
Secretin & Methacholine	A. Patients without pancreatic disease				
	1. Skin grafting	58	64	52	54
	2. Pneumonia	47	38	44	48
	3. Arteriosclerotic heart disease	28	26	40	28
	4. Carcinoma transverse colon	98	102	82	92
	5. Coronary occlusion	44	48	36	40
	6. Gastric ulcer	42	42	30	30
	7. After inguinal hernioplasty	84	76	74	76
	8. Chronic duodenal ulcer	102	110	92	92
	9. Psychoneurosis	92	102	100	104
	10. Mucous colitis	42	40	42	40
	11. Chronic cystic mastitis	68	96	112	72
	12. Postcholecystectomy syndrome	184	178	176	176
	13. After appendectomy	77	87	79	92
	14. Virus pneumonia	76	96	96	102
	15. Tenosynovitis	115	113	110	107
	Average, 15 cases	77	81	78	77
	B. Patients with pancreatic disease				
	1. Acute pancreatitis	240	372	312	338
	2. Carcinoma pancreas	24	38	40	32
	3. Carcinoma head pancreas	24	14	20	30
	4. Carcinoma head pancreas	68	68	78	83
	5. Acute pancreatitis	104	284	278	262
	6. Chronic pancreatitis	80	86	86	84
	7. Pancreatic calcinosis	76	74	74	76
	8. Chronic pancreatitis, postcholecystectomy syndrome	134	132	138	120
	9. Acute pancreatitis	96	94	94	99
	10. Acute pancreatitis	52	72	66	66
	11. Chronic relapsing pancreatitis	74	79	86	85
	Average, 11 cases	88	119	116	116

TABLE 2.—*Serum Amylase Response Data After Various Pancreatic Secretagogues in Patients With and Without Pancreatic Disease*—Continued

Drug	Diagnosis	Serum Amylase Response to Drug, Mg./100 Cc. Glucose			
		Control	1 Hr.	2 Hr.	3 Hr.
Secretin & Morphine & Methacholine	A. Patients without pancreatic disease				
	1. Chronic ulcerative colitis	116	122	142	162
	2. Carcinoma breast	86	84	92	94
	3. Diabetes mellitus	78	78	75	76
	4. After herniorrhaphy	95	102	96	96
	5. Pernicious anemia	56	72	70	84
	6. After appendectomy	142	125	127	120
	7. Postcholecystectomy syndrome	102	108	114	114
	8. Postcholecystectomy syndrome	72	75	72	72
	9. Chronic cystic mastitis	68	78	87	96
	10. Chronic cholecystitis	96	90	90	98
	11. Regional ileitis	135	145	192	198
	12. Carcinoma lung	84	88	86	116
	13. Cardiospasm	62	134	138	142
	14. Rheumatoid arthritis	76	76	142	120
	Average, 14 cases	91	98	109	111
	B. Patients with pancreatic disease				
	1. Acute pancreatitis	194	256	306	216
	2. Chronic relapsing pancreatitis	56	66	68	82
	3. Pancreatic calcinosis	34	38	32	30
	4. Acute pancreatitis	95	98	118	98
	5. Carcinoma head pancreas	117	110	115	127
	6. Carcinoma head pancreas	85	85	85	85
	7. Carcinoma papilla vater	78	74	79	88
	8. Acute pancreatitis	96	84	82	86
	9. Chronic pancreatitis	69	74	82	78
	10. Acute and chronic pancreatitis	102	196	302	188
	11. Pancreatic calcinosis	46	46	62	49
	12. Pancreatic calcinosis	84	112	68	76
	Average, 12 cases	88	119	116	116

amylase rises in 4 patients. These four patients had cancer of the head of the pancreas, a pancreatic abscess (after drainage), chronic relapsing pancreatitis, and subacute pancreatitis. The elevations obtained were from 115 to 206 mg., from 136 to 284 mg., from 47 to 164 mg., and from 184 to 315 mg., per 100 cc.

Bethanechol.—Bethanechol was administered to 12 control patients and to 10 patients with pancreatic disturbances. Three instances of elevated blood amylase were found in each group. The rises in all cases were of small magnitude. The changes in blood amylase observed in patients without pancreatic disease were from 58 to 96 mg., from 76 to 114 mg., and from 86 to 126 mg., per 100 cc. Among the patients with pancreatic disorders, rises were noted in a case of acute pancreatitis, in one of chronic pancreatitis following internal drainage of a pancreatic cyst, and in a patient with chronic pancreatitis with a cyst of the head of the pancreas. The corresponding elevations found were from 178 to 246 mg., from 65 to 138 mg., and from 125 to 161 mg., per 100 cc.

Secretin and Morphine.—Secretin and morphine when combined produced an amylase elevation in 1 out of a group of 17 control patients. The rise was from 53 to 114 mg. per 100 cc. Among 13 patients with chronic pancreatic disease, 4 positive responses were observed: One patient had chronic pancreatitis, one had cancer of the body of the pancreas, one had acute pancreatitis, and one had had a pancreatic

abscess drained. The recorded changes in blood amylase levels were, respectively, from 78 to 216 mg., from 182 to 312 mg., from 132 to 214 mg., and from 114 to 135 mg., per 100 cc.

Secretin and Methacholine.—The secretin-methacholine combination evoked no alteration in the blood amylase levels in 15 patients without pancreatic disease. Two instances of amylase elevations, however, were seen in a group of 11 patients with pancreatic disease. Both patients had acute pancreatitis. The amylase changes observed were from 240 to 372 mg. and from 104 to 284 mg. per 100 cc.

Secretin, Methacholine, and Morphine.—Secretin, methacholine, and morphine used in combination were the most potent stimulus for provoking elevations in blood amylase. Seven of 14 control patients evidenced this rise. Among the 12 patients with pancreatic disease, positive changes were obtained in 3 patients, with acute pancreatitis, chronic relapsing pancreatitis, and acute and chronic pancreatitis. The rises noted were from 194 to 306 mg., from 56 to 82 mg., and from 102 to 302 mg., per 100 cc., respectively.

COMMENT

The results of this investigation indicate clearly that pancreatic secretagogues and sphincter-tonic drugs, singly or in combinations, are capable of evoking small transient elevations in the blood amylase. This can best be illustrated by plotting the average period blood amylase values for each drug in the control and abnormal groups (pancreatic disease), as is done in Table 3 and its accompanying charts. These alterations in blood amylase level appear to occur in an unpredictable fashion in patients with and without pancreatic disease. Because of this behavior, it seems impossible to establish any criteria which might enable one to utilize these responses in the diagnosis of pancreatic disease.

The recorded observations for the various drugs used by previous investigators have been combined and summarized in Table 4. In general, this composite is in agreement with the results of the present study. Elevations have been observed to be present or absent both in patients with and in those without proved pancreatic disease. In the case of neostigmine and neostigmine and morphine, such lack of correlation of clinical diagnosis and laboratory study has not yet been reported. But there is no reason to assume that these drugs behave in a manner different from those which have been more extensively studied. Indeed, Harvey and Butcher [63] have just reported an experimental investigation in animals in which they observed such unpredictable responses to neostigmine following ligation of the pancreatic duct and also in the intact animal that the conclusion was drawn that neostigmine could not be used in the diagnosis of pancreatic disease.

The conclusions drawn by previous investigators as to the possible diagnostic value of the serum enzyme tests have been markedly divergent. Among those who felt that the tests show promise of diagnostic importance were Burke,[59] Lopusniak,[56] Sanchez-Ubeda,[61] and Malinowski.[62] On the other hand, Wirts,[8] Sachar,[58] and Royer [41] have expressed doubts of its diagnostic possibilities.

From the results of these studies and from purely theoretical considerations, the conclusion seems justified that the provocative blood enzyme tests will be of little diagnostic importance. As Sachar [58] has so aptly expressed it, the feasibility

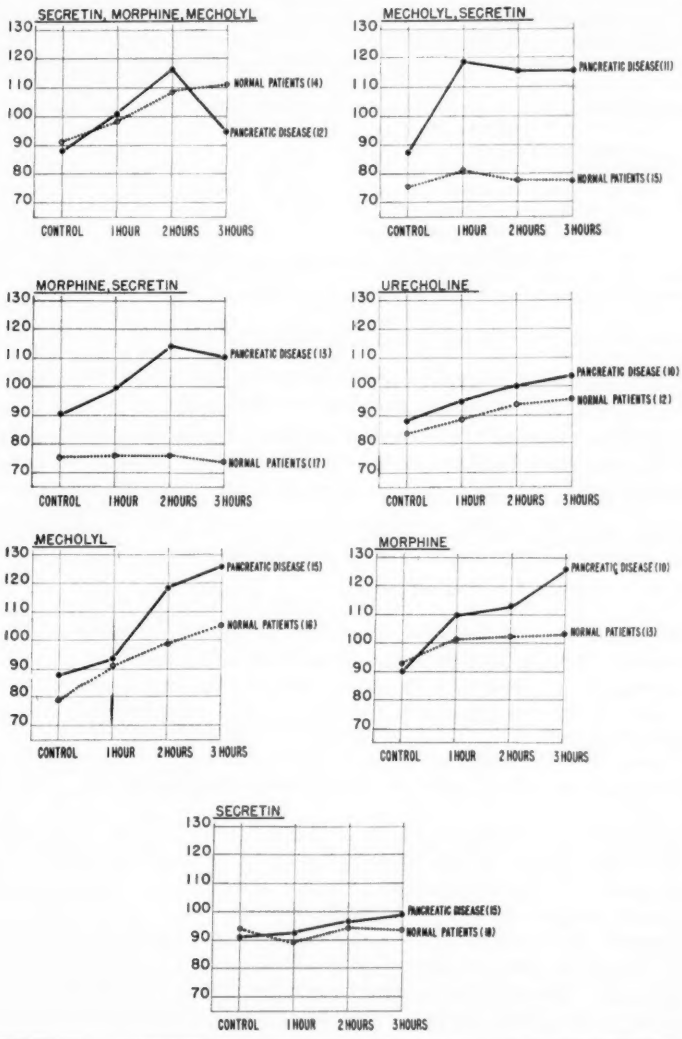
of serum enzyme tests depends upon finding a pancreatic stimulant which will satisfy the following criteria: (1) The stimulant invariably causes the serum amylase concentration of normal persons to rise. The failure, then, of the serum amylase to rise would indicate a pancreatic insufficiency and a diagnosis of chronic pancreatitis. Or (2) the stimulus causes no elevation of the serum enzyme in normal persons, but when the pancreatic duct is blocked it does cause an elevation. A rise in enzymes, then, indicates obstruction of the pancreatic duct, as seen in carcinoma or in pancreatic edema. The best combination of responses is postulated by Wirts and Snape,[8] who observed three patterns: (1) no rise, in advanced pancreatic fibrosis; (2) moderate elevations, in normal patients, and (3) marked elevations, in pancreatic duct obstructions. At most, then, there are three patterns of response, regardless of whether a hydrosecretagogue, an enzyme stimulus, or a sphincter-tonic drug is used singly or in combination. In any subject upon whom a serum enzyme test is being done, there are four unknown variables upon which the type of response obtained depends. First, there is the functional state of the sphincter of Oddi. Second, there must be considered the patency of the pancreatic duct system. Included in this variable are the site of obstruction and the degree of development of collateral anastomoses between the main and accessory pancreatic duct systems. Indeed, congenital anatomical factors may vitiate the effect of pancreatic duct obstruction. Spasm of the sphincter and pancreatic duct obstruction tend to elevate the blood enzyme levels after stimulation. The third variable is the

TABLE 3.—*Average Serum Amylase Response Values in Patients With and Without Pancreatic Disease Following Various Pancreatic Stimulants*

	Cases, No.	Average Serum Amylase Values * Mg./100 Cc. Glucose			
		Control	1 Hr.	2 Hr.	3 Hr.
Morphine					
Patients without pancreatic disease	13	92	102	103	103
Patients with pancreatic disease	10	90	110	113	123
Secretin					
Patients without pancreatic disease	18	93	89	93	92
Patients with pancreatic disease	15	91	92	96	98
Methacholine					
Patients without pancreatic disease	16	79	91	98	105
Patients with pancreatic disease	15	88	104	117	126
Bethanechol					
Patients without pancreatic disease	12	84	88	94	96
Patients with pancreatic disease	10	88	95	100	104
Secretin & morphine					
Patients without pancreatic disease	17	75	78	78	74
Patients with pancreatic disease	13	91	99	114	110
Secretin & methacholine					
Patients without pancreatic disease	15	77	81	78	77
Patients with pancreatic disease	11	88	119	116	116
Secretin, morphine, & methacholine					
Patients without pancreatic disease	14	91	98	109	111
Patients with pancreatic disease	12	88	103	117	95

* The average serum amylase values are presented in graph form in the accompanying charts (p. 209).

presence or absence of inflammation in the secreting glandular tissue. When inflammation is present, the enzyme partition between the duct and blood stream appears to be disturbed, so that elevation of the blood enzymes is favored. Finally, the fourth variable is the extent of destruction of acinar tissue. When this is extensive, be it



by tumor or by fibrosis, the ability to secrete enzymes is much diminished and the enzyme response tends to be depressed. Now, the response in any individual case is the summation of the four disparate factors. It seems clear, from the mathematical point of view, that with four independent variables and three response patterns only an indefinite relationship can be postulated.

TABLE 4.—*Composite Summary of Serum Enzyme Responses to Various Drugs as Reported by Previous Investigators*

Stimulant	Enzyme Responses *	
	Normal Patients	Patients with Pancreas Disorders
1. Carbaminocholine	±	—
2. Secretin	±	±
3. Methacholine	±	..
4. Bethanechol	+	± †
5. Neostigmine	—	±
6. Secretin & morphine	+	—
7. Secretin & methacholine	±	±
8. Bethanechol & morphine	+	..
9. Neostigmine & morphine	±	—
10. Carbaminocholine & morphine	±	..
11. Secretin, morphine, & methacholine	+	±

* Amylase and lipase were studied; +, elevation; —, no elevation; ±, variable.
† Elevations if pancreatic duct obstructed; no elevations otherwise.

SUMMARY AND CONCLUSIONS

The literature of the so-called provocative serum enzyme tests suggested for diagnosis in pancreatic disease is reviewed and assessed.

An experimental study is presented of the blood amylase responses to morphine, secretin, methacholine (Mecholyl), and bethanechol (Urecholine), singly and in combination, in 192 patients with and without proved pancreatic disease.

An analysis of the results of this investigation leads to the conclusion that these serum enzyme response tests have no value in the diagnosis of pancreatic disorders.

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CLINICAL EXPERIENCE WITH COUMARIN ANTICOAGULANTS WARFARIN AND WARFARIN SODIUM

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SYNTHESIS of the 3-substituted-4-hydroxycoumarin anticoagulant No. 42, 3-(α phenyl-β-acetylethyl)-4-hydroxycoumarin,* was first accomplished and its action studied in Dr. Karl Paul Link's laboratory.† The compound has been generically termed "warfarin" and its sodium salt termed "warfarin sodium." The sodium derivative [4] is readily water-soluble, and the solutions are stable. Structural formulae of these compounds appear in Figure 1. Warfarin, when given orally, and warfarin sodium, when given orally or intravenously, produce hypoprothrombinemia, as do the other 3-substituted-4-hydroxycoumarin compounds.

Interesting experimental data regarding warfarin sodium and warfarin in the rat have been made available by Eble,‡ working in Link's laboratory. These workers believe the rat to be the preferred experimental animal in the study of 4-hydroxycoumarin anticoagulants, as the response of the rat is most closely parallel to that of the human. Eble found that when massive oral doses, of 100 mg. per kilogram, of warfarin were given the rat its presence in the plasma could be detected spectrophotometrically (Beckman, 308 mm.) within four hours. The plasma concentration time curve was not affected by simultaneous doses of vitamin K_1 (250 mg. per kilogram). However, in adequate doses vitamin K_1 gave complete protection from the toxicity and anticoagulant activity of warfarin and was more effective in this respect against warfarin than against cyclocumarol.

Lower doses of warfarin resulted in proportionately lower concentrations of warfarin in the plasma. There was no difference between warfarin and its sodium salt in the rate of appearance in the blood stream or in the ultimate concentration when they were given orally.

It was found that warfarin sodium given intravenously rapidly diffused through the rat body and was found in maximum concentration in the muscle, plasma, and liver five minutes after the injection. When the gastric pyloric sphincter

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The warfarin (Coumadin) sodium was prepared in ampoules by Dr. Samuel Gordon, Endo Products, Inc., Richmond Hill, N. Y., from material supplied by Prof. Karl Paul Link.

* The chemical name 3-(α acetonylbenzyl)-4-hydroxycoumarin is the systematic name used by *Chemical Abstracts*.[5]

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‡ Eble, J. N.: Doctoral Dissertation, University of Wisconsin, to be published. This material was obtained through personal communication from Prof. Karl Paul Link.

was ligated, it was observed that warfarin entered the blood stream through the stomach wall. The effect of large continuous doses of warfarin given orally, which in the absence of vitamin K_1 are fatal, could be abolished by an adequate dose of vitamin K_1 given simultaneously. Menadione (2-methyl-1,4-naphthoquinone) was found to be less effective.

MATERIAL AND PROCEDURES

This is a report of intravenous administrations of warfarin sodium to 20 patients and of oral administrations of warfarin and warfarin sodium to 16 patients in the University Hospitals, Madison, Wis. Twenty-one patients of the total number received maintenance therapy with warfarin or warfarin sodium orally for a variable period of time (10 days to 6 weeks). Warfarin sodium was administered intravenously in aqueous solution containing 7.5 mg. per milliliter. Warfarin and warfarin sodium were given by mouth in 25 mg. scored tablets.

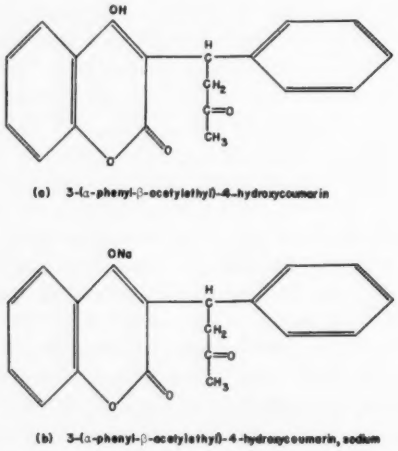

Fig. 1.—(*a*) Warfarin; (*b*) warfarin sodium.

Twenty-five patients who received these preparations had evidence of thromboembolic disease, their diagnoses including myocardial infarction, pulmonary embolism, thrombophlebitis, and phlebothrombosis. In 11 patients in whom there was no evidence of thromboembolic disease, the diagnoses included carcinomas of the breast, cervix, lip, and tongue and diabetes mellitus. Ages of the patients ranged from 34 to 77 years, with the exception of one patient who was 14 years old.

Determinations of prothrombin times were performed on 100% plasma by the one-stage method of Quick,[3] using Difco thromboplastin (rabbit brain). For each patient all prothrombin studies were performed daily at approximately the same time. Control prothrombin times were usually 12 seconds, rarely 11 and 13 seconds, which were taken to represent 100% of normal. Results were reported in seconds and percentage of normal. In the 21 patients receiving maintenance doses of warfarin or warfarin sodium, after initiation of hypoprothrombinemia with the larger intravenous or oral initial dose, an attempt was made to keep the prothrombin values between 25 seconds (20% of normal) and 17 seconds (40% of normal) as a satisfactory therapeutic range. In eight patients, observations for possible toxicity were made in that complete blood cell counts, urinalyses, and hepatic function studies (thymol turbidity, cephalin-cholesterol flocculation, alkaline phosphatase, serum albumin and globulin, serum bilirubin, and sulfobromophthalein [Bromsulphalein] retention determinations) were done. We found no evidence of toxicity on the basis of these studies.

The initial dose of anticoagulant, whether oral or intravenous, was 1 mg. per kilogram of body weight, the drug usually being given to the nearest 5 mg. Subsequent dosage of anticoagulant by mouth was governed by the prothrombin time and was given after the peak effect of the initial dose had been reached, usually on the third or fourth day (except in two of the earlier cases of oral administration of initial dose, when subsequent arbitrary daily doses were given and it became obvious that the hypoprothrombinemia was too great).

RESULTS

Intravenous Administration.—Twenty patients received initial doses of 1 mg. per kilogram of body weight of warfarin sodium intravenously, the doses varying from 45 mg. to 90 mg. Hypoprothrombinemia within the therapeutic range was present in 20 to 24 hours in 16 patients, and 5 of the 16 patients had reached the therapeutic range within 16 hours. By 36 hours the remaining four patients

TABLE 1.—*Effect of Single Intravenous Injection of Warfarin Sodium*

Patient No.	Dosage, Mg.	Prothrombin Time				
		Latent Period, Hr.	Therapeutic Range		Return to Normal, Days	Peak Effect, Days
			Hours to Achieve	Duration, Days		
1	55	16	20	(2)*	(4)*	2
2	70	8	16	(4)*	(6)*	3
3	70	8	16	2	10	1
4	50	8	20	1	5	2
5	50	14	24	5	9	3
6	50	12†	24	2	5	2
7	75	16	36	4	8	3
8	70	16	36	7	11	3
9	60	16	36	(1)*	(3)*	2
10	90	16†	16	...‡	...‡	2
11	90	16†	24	...	...	2
12	60	16†	24	...	...	2
13	85	12†	20	...	...	3
14	85	20	36	...	...	2
15	75	16†	20	...	...	3
16	75	16†	20	...	...	3
17	70	16†	16	...	...	3
18	75	16†	16	...	...	3
19	45	16†	20	(3)*	(5)*	3
20	65	20†	24	...	...	2

* Patients 1, 2, 9, and 19 received vitamin K_1; thus the figures parenthetically enclosed are altered on this basis.

† Initial prothrombin time not determined at an earlier hour.

‡ Patients 10 through 18 and patient 20 were maintained on the oral preparation for variable periods.

had achieved the therapeutic range; in one of these the prothrombin time remained at the upper level of the therapeutic range only briefly and then returned toward normal. The control prothrombin time was 12 seconds, or 100% of normal, in each instance prior to the administration of the drug. Serial prothrombin time determinations revealed a latent period of 8 to 16 hours in all but one patient, in whom this was delayed to 20 hours. A maximal effect usually occurred in 48 to 72 hours. A single dose produced a discernible effect for 5 to 10 days before return to the normal prothrombin time. Obviously this drug does not preclude the necessity for associated use of heparin when immediate anticoagulant action is desired, but heparin can ordinarily be discontinued safely in 24 hours. A summary of the effects is shown in Table 1.

Our first patient received sodium menadiol diphosphate (Synkayvite Sodium Diphosphate, Hoffmann-LaRoche) on the second day to counteract an excessively prolonged prothrombin time and 24 hours later received vitamin K_1; this patient was later found to have metastatic liver disease from carcinoma of the breast. Our second patient was given vitamin K_1 intravenously on the fifth day for continuing prolongation of the prothrombin time. The 9th and 19th patients were

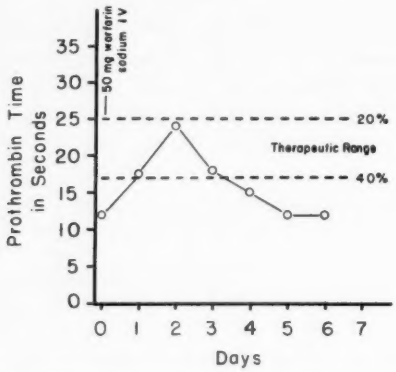

Fig. 2.—Effect of a single injection of warfarin sodium intravenously, 1 mg. per kilogram.

TABLE 2.—*Effect of Oral Administration of Warfarin or Warfarin Sodium*

Patient No.	Dosage, Mg.	Prothrombin Time: Hours to Achieve Therapeutic Range	Prothrombin Time: Peak Effect, Days
21	50	24	2
22	62.5	24	2
23	75	24	3
24	62.5	24	2
25*	75	24	2
26*	87.5	36†	2
27*	80	24	3
28*	80	24	3
29*	70	16	3
30*	50	20	2
31*	50	24	2
32*	95	20	3
33	65	24	3
34*	65	24	3
35*	75	24	2
36*	65	20	3

* Continued on maintenance therapy.
† Prothrombin time inadvertently not determined at 24 hours.

given vitamin K_1 intravenously on the third day. Our 10th through 18th and also the 20th patients all received additional maintenance doses of warfarin or warfarin sodium orally; later, the 11th patient received vitamin K_1 on the ninth day, while the 13th patient received vitamin K on the seventh day, in both instances to counteract hypoprothrombinemia rapidly. Figure 2 shows a typical effect of a single intravenous injection of warfarin sodium.

Oral Administration.—Six patients initially received warfarin orally, and the hypoprothrombinemic effect was observed; two of these were among the earlier patients seen, and they received additional daily doses immediately (before peak hypoprothrombinemic effect of the initial dose) and subsequently had excessive hypoprothrombinemia, which necessitated administration of intravenous vitamin K_1. No hemorrhagic or toxic effects were observed, even though one of the patients received 150 mg. of warfarin in a 48-hour period. Ten patients initially received warfarin sodium orally, and the hypoprothrombinemic effect was observed.

After initial oral administration of the preparations to these 16 patients, 15 had prolongation of the prothrombin time to the therapeutic range by 24 hours. Inadvertently, for one patient the prothrombin time was not determined at 24 hours, but it was well within the therapeutic range by 36 hours. Table 2 contains a summary of these effects of orally administered warfarin and warfarin sodium. Figure 3 shows the effect of warfarin with both initial and maintenance therapy.

Intravenous and Oral Administration.—Ten patients received maintenance doses of warfarin or warfarin sodium orally after the initial hypoprothrombinemia had been achieved by warfarin sodium intravenously. Maintenance dosage of warfarin or warfarin sodium was required, usually daily, every other day, or occasionally only every third day, in doses of 12.5 mg. or 25 mg., according to the prothrombin time, none being administered if the prothrombin time was 25 seconds (20%) or less. Figure 4 shows the effect in a typical patient of warfarin sodium given intravenously followed by doses of warfarin orally to maintain hypoprothrombinemia.

Effect of Vitamin K and Vitamin K_1.—Sodium menadiol diphosphate, the hexahydrate of the tetrasodium salt of 2-methyl-1,4-naphthalenediol diphosphate, a synthetic vitamin K analogue, was administered to two patients, to one intravenously and to the other intramuscularly, in a dosage of 75 mg. The intravenous administration changed the values from 46 seconds (12%) to 23 seconds (23%) within 18 hours; the intramuscular injection changed values from 22 seconds (20%) to 16 seconds (32%) within 12 hours and to 14 seconds (62%) by 36 hours.

Vitamin K_1 (Mephyton),§ 2-methyl-3-phytyl-1,4-naphthoquinone, was administered in single doses intravenously in 25 mg. to 100 mg. amounts to 11 patients with hypoprothrombinemia. Five had values significantly beyond the therapeutic range (80 seconds [4%] to 44 seconds [10%]), and three of these patients, for whom determinations were done, had values well within the therapeutic range by 4 hours; all values were nearly 100% by 18 hours after the vitamin K_1 administration. In the other six patients, values, which had been within the therapeutic range, were well above the therapeutic range and were normal, or nearly normal, by 18 hours. Table 3 presents a summary of the effects of vitamin K_1.

Toxicity.—In addition to the studies for toxicity reported under "Material and Procedures," our observations for toxicity were confined largely to hemorrhagic manifestations, in essence the presence or absence of microscopic hematuria. In one instance vitamin K_1 was given as an antidote because of marked prolongation of the prothrombin time (80 seconds [4% of normal]), and at this level there was evidence of microscopic hematuria; later, after maintenance therapy had been

§ The vitamin K_1 used in this study was supplied by Merck & Co., Inc., Rahway, N. J.

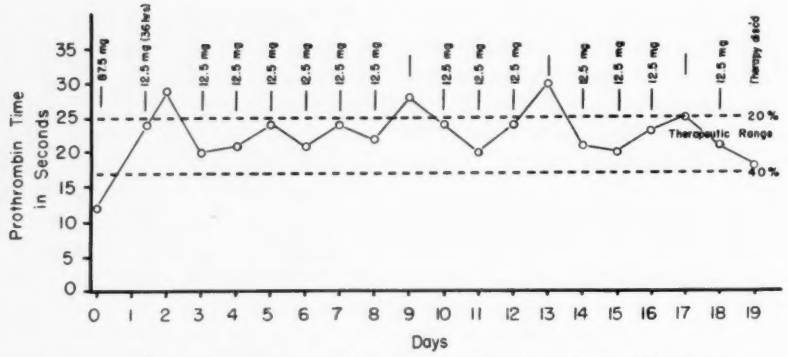

Fig. 3.—Anticoagulant therapy initiated and maintained with warfarin orally.

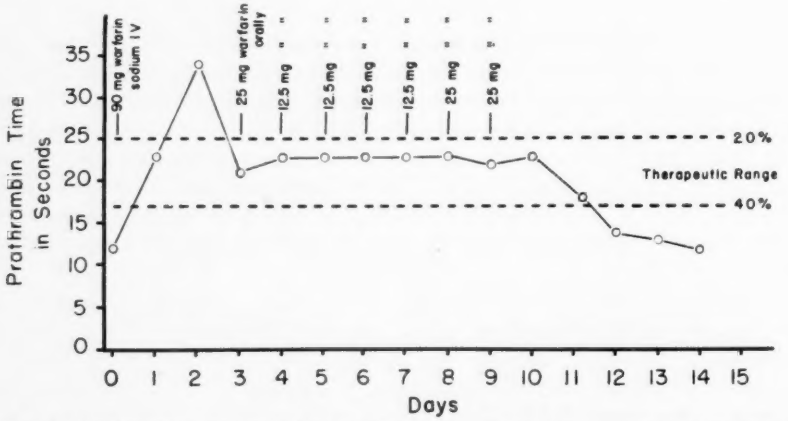

Fig. 4.—Anticoagulant therapy initiated with warfarin sodium intravenously and maintained with warfarin orally.

TABLE 3.—*Effect of Intravenous Vitamin K_1 on Hypoprothrombinemia Induced by Warfarin and Warfarin Sodium*

Patient No.	Vitamin K_1 Dosage, Mg.	Prothrombin Time * Before Vitamin K_1 Seconds	Before Vitamin K_1 %	After Vitamin K_1 Seconds	After Vitamin K_1 %	Hours
1.	50	23	23	13	77	12
2.	50	45	9	17	40	8
				14	62	18
9.	50	15	52	12	100	4
12.	50	29	21	12	100	4
18.	25	80	4	24	22	4
				15	52	18
19.	90	44	10	17	40	4
				12.5	90	18
21.	100	40	11	14	62	12
				12	100	24
23.	25	51	8	18	35	4
				13	77	14
24.	50	27	18	12	100	16
25.	100	44	10	14	62	14
33.	50	25	20	16	45	4
				12	100	18

* Recorded in seconds and per cent of normal.

reinstituted for three weeks, vitamin K_1 was given intravenously because of gross hematuria. Additionally, of the total of 21 patients on maintenance therapy, 2 showed intermittent microscopic hematuria, 4 had microscopic hematuria both before and during the anticoagulant therapy without change in degree while on therapy, and 3 with indwelling urethral catheters had intermittent microscopic hematuria while on anticoagulant therapy.

COMMENT

Warfarin and warfarin sodium compare favorably with the other coumarin anticoagulants. The latent period and the time required to produce therapeutic hypoprothrombinemia are similar to those with ethyl biscoumacetate (Tromexan ethyl acetate), but the duration of action is more prolonged and it is less difficult to maintain a controlled stable level of hypoprothrombinemia. The latent period and time required to achieve therapeutic hypoprothrombinemia are shorter than those with either cyclocumarol (Cumopyran) or bishydroxycoumarin (Dicumarol), while the duration of the effect is similar. Comparison of potency milligram for milligram reveals a higher anticoagulant activity for warfarin and warfarin sodium, the therapeutically effective dose in milligram of anticoagulant per kilogram of body weight being the lowest of all. As is true with the other coumarin anticoagulants, frequent prothrombin time determinations are required. The maintenance dose depends on the prothrombin time for that day and on whether the value is rising or falling.

From study of Tables 1 and 2, comparing the onset of effect and duration of effect after 1 mg. per kilogram doses of warfarin sodium intravenously and warfarin or warfarin sodium orally, there would appear to be no advantage to using the anticoagulant intravenously except when the patient is vomiting or cannot otherwise tolerate oral medication. However, intravenous warfarin sodium does have a place in therapy for occasional patients. It would seem that, if necessitated by intolerance of the patient for oral medication subsequent to initial dosage, warfarin sodium could be given in these same small doses intravenously daily for as long as necessary. However, we have not yet attempted to demonstrate this in any of our patients. Onset, peak effect, and duration of hypoprothrombinemia are quite similar after either route of administration; therefore, gastrointestinal absorption of warfarin must be rapid and complete. From analysis of Figures 2, 3, and 4 and Tables 1 and 2, it may be seen that possibly warfarin and warfarin sodium, whether used alone or together, may be the most satisfactory anticoagulants[7] of coumarin type so far available. However, further experience is necessary for more complete evaluation.

Vitamin K_1 was used most in this study and proved to be a very effective antidote for hypoprothrombinemia induced by warfarin sodium and warfarin. Experience has shown that mere prolongation of the prothrombin time beyond the therapeutic range does not constitute an immediate indication for the use of an antidote. When necessary, however, vitamin K_1 is very effective.

In general, our results confirmed the recent observations of Shapiro[6] and Wolff, Barker, Gifford, and Mann.[8] Although the dose of 1 mg. per kilogram of body weight is optimal, we favor using 75 mg. of the anticoagulant as a maximum dose, since we saw excessive hypoprothrombinemia with larger dosage, dependent on body weight. It was likewise our experience that maintenance doses

should be given after the peak effect of the initial administration of drug has been achieved. Hypersensitivity to the drug was seen in three patients. One subsequently was found to have metastatic liver involvement, but the other two showed continued and progressive hypoprothrombinemia after administration of warfarin sodium without any other obvious influencing factors. We have not hesitated to give this compound, when indicated, to patients with microscopic hematuria due to certain causes such as an indwelling urethral catheter.

CONCLUSIONS

Intravenous warfarin sodium induced therapeutic hypoprothrombinemia safely and effectively in 20 patients. Warfarin or warfarin sodium orally induced an effective hypoprothrombinemia in 16 patients, with a similar time of onset and duration. The initial dose for either drug was 1 mg. per kilogram of body weight; however, we now conclude that an initial dose should not exceed 75 mg., regardless of body weight.

There would appear to be no advantage to use of warfarin sodium intravenously rather than warfarin or warfarin sodium orally, except when the patient is vomiting or cannot otherwise tolerate oral medication. We think, however, that for occasional patients intravenous administration of this drug does have a place in therapy.

Maintenance of therapeutic hypoprothrombinemia was accomplished with ease in 21 patients by using warfarin or warfarin sodium orally. Warfarin appears to have no advantage over warfarin sodium.

As with other 4-hydroxycoumarin compounds, microscopic hematuria is occasionally seen as a toxic manifestation, and one must watch for this as well as other evidences of hemorrhage.

Vitamin K_1 is a very effective antidote against hypoprothrombinemia induced by warfarin sodium and warfarin.

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PORPHYRIA

A Clinical and Neuropathologic Report

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PORPHYRIA is considered to be an "inborn error" in the metabolism of the porphyrins.* Many of its clinical manifestations are neurologic or psychiatric or both. Indeed, it does not seem to be unusual to have the metabolic disorder discovered only after the neuropsychiatric symptoms have developed. This imposes a responsibility on the part of the physician to be alert to the possibility of such a process in appropriate neurologic and psychiatric cases and to be acquainted with the symptoms and signs produced by this disorder of pyrrole metabolism. For this reason, we wish to report three cases illustrating the different clinical features of the disease and the neuropathologic changes observed in two of them.

REPORT OF CASES

CASE 1.—N. T., a Negro girl, aged 17, was admitted to the hospital on April 9, 1944, complaining of vomiting and pain in the right side of her abdomen. These symptoms had developed quite suddenly on April 5 and had persisted so that she had been sent into the hospital with a diagnosis of "acute appendicitis" or some "acute inflammatory disease" in the "pelvis." For about a year before this, she was said to have had recurrent attacks of abdominal pain, but they were never so severe or so prolonged as the present attack. She also claimed to have had a similar pain, but milder, on the second or third day of her menstruation. Before the present illness, she had had some nocturia, and since the onset she had experienced painful, difficult urination.

Her mother, father, three brothers, and three sisters were apparently healthy.

The physical examination on admission revealed the abdomen to be soft and relaxed. There was tenderness on deep pressure over the whole abdomen, more marked in the right lower quadrant. Peristalsis was felt to be decreased. The neurologic examination was essentially negative at this time.

On admission, the temperature was 99.4 F., pulse rate 98 per minute, and respiratory rate 24 per minute. The blood pressure on April 12 was 145/105.

Laboratory Studies on Admission.—Erythrocytes were 4,130,000 per cubic millimeter of blood and leucocytes 13,550; of the latter 77% were neutrophiles, 21% were lymphocytes, and 2% were monocytes. The urine was red-brown in color and showed a specific gravity of 1.035, a slight trace of albumin, no sugar, a negative benzidine test, no erythrocytes, and 5 to 8 leukocytes per high-power field. The sedimentation rate was 40 mm. in an hour.

From the Department of Neurology, University of Pennsylvania School of Medicine; supported in part by the Kirby-McCarthy Fund.

* References 1-3.

Course in Hospital.—On April 9 an appendectomy was performed. Nothing abnormal was noted in the pelvic organs. The lumen of the appendix was patent, and the tip was greatly distended by fecal material. The mucosa of the appendix showed no change; the submucosa was atrophic and showed some recent hemorrhages. The whole structure was hyperemic.

Postoperatively the patient began to have difficulties of an emotional nature. She complained constantly of numerous vague pains and aches. She had outbursts of crying for no reason. She often pulled the sheets over her head "to get some sleep." She complained of blurred vision and diplopia. The ophthalmologist found only small and attenuated "retinal arteries." On April 14 her blood pressure was 198/108. She continued to be confused and exhibited further erratic behavior. On April 17 it was found that her wound had broken open and a second closure of the abdominal wound was done. From here on it was felt imperative that she be kept well sedated. Some secobarbital (Seconal) was given immediately after the appendectomy, but later phenobarbital and amobarbital (Amytal) sodium were used with other sedatives to try to control her.

By April 22 she was stuporous. By April 26 she was hallucinating, markedly weak, and comatose most of the time. The following day she was generally weaker, and by the next day she did not move at all; consequently an ascending paralysis was suspected. She died on April 28.

Other Laboratory Studies on the Patient.—The urine was frequently examined. The color was variously reported as "red," "brown," "orange," and "burgundy red." In only one urine specimen were erythrocytes seen with a positive benzidine test. On April 25 her urine gave a positive response for urobilinogen in dilutions from 1:10 to 1:100, but the results were held to be uncertain. On April 28 a spectroscopic examination of the urine showed an absorption band indicating the presence of uroporphyrin.

On April 25 the icterus index was 5. The direct van den Bergh test gave no reaction, while the indirect reaction was less than 1 mg. per 100 cc.

On April 12 no sickling of erythrocytes was noted.

On April 13, the blood sugar was 90 mg. and the blood urea nitrogen was 16 mg. per 100 cc. On April 27 the blood urea nitrogen was 32 mg. per 100 cc.

On April 9 the blood Wassermann and Kahn tests were negative.

Pathologic Findings.—The general autopsy disclosed a fibrinous peritonitis at the site of the appendectomy as the only significant finding.

Examination of the Nervous System: Gross description (Dr. Francis Forster). The cerebral hemispheres were symmetrical. There were no changes in the gyri or sulci. The arachnoid over the vertex was clear and translucent. There were no changes noted in the vessels or in the meninges of the base of the brain. Coronal sections of the cerebral hemispheres revealed that the cortical gray matter and basal ganglia were dark pink in color, with prominence of the blood vessels. This was particularly so in the thalamus but to a lesser extent in the putamen. The brain stem, cerebellum, and spinal cord were externally normal and when sectioned failed to reveal any changes.

Microscopic examination (Dr. Bernard J. Alpers). After fixation in formalin, celloidin sections were made of various parts of the central nervous system and were stained with hemotoxylin and eosin, the Weigert stain, and the Nissl technique.

The meninges over the cerebral cortex contained a thin scattering of fresh red blood cells, without evidence of phagocytosis or hemosiderin deposition. The meningeal and parenchymal blood vessels were normal. However, an occasional deposition of a yellow pigment was seen in the blood vessel wall or the Virchow-Robin space. When in the blood vessel wall, the pigment lay free and was also within the tissue composing the adventitia. This deposition of pigment occurred only in the parenchymal vessels—in the cortex and basal ganglia.

The neurones of the cortex (blocks were taken from left frontal, right orbital, right temporal, right parietal, and left motor areas) showed well-marked acute toxic changes with fragmentation, paling and dispersal of the Nissl substance, and swelling of the cell bodies.

There were recent scattered perivascular hemorrhages noted, especially in the floor of the fourth ventricle and near the lateral recesses of that ventricle. There was one fairly large recent, but not definitely perivascular, hemorrhage in the medial wall of the basis pedunculi, medial to the substantia nigra. This had dissected ventrally.

The blood vessels in the meninges of the spinal cord were dilated and engorged, as were those of the spinal nerve roots. Within the substance of the spinal cord there were engorgement and dilatation of the blood vessels, with occasional fresh perivascular hemorrhages. There was some decrease in the number of anterior horn cells. Some of the remaining anterior horn cells were well preserved, but most of them stained darkly, with loss of distinct Nissl granules. Most anterior horn cells had lost their nuclei, and many of their processes were attenuated.

There was no evidence of demyelinization in the cerebrum, basal ganglia, brain stem, or spinal roots.

CASE 2.—E. T., a Negro girl, aged 20, sister of N. T. (Case 1), was admitted to the hospital on April 16, 1944. She had become nauseated on April 13. She took some medicine for her "indigestion" and went to bed. She awakened in the morning of April 14 with a sharp pain in the right lower quadrant of the abdomen. Vomiting began. The abdominal pain increased in severity; the nausea and vomiting persisted.

On admission, the blood pressure was 90/45, temperature 99.6 F., pulse rate 84 per minute, and respiratory rate 20 per minute. There was a slight rigidity of the muscles of the right lower quadrant of the abdomen. Deep pressure of the left lower quadrant produced pain in the right lower quadrant. Peristalsis was "normal." A brief neurolgic examination at this time showed only generally "hyperactive" reflexes.

An appendectomy was performed on April 16. The appendix was "slightly injected," and its lumen was closed. Histologic section showed "atrophy of the mucosa" and an "old hyalinized fibrous thickening of the submucosa."

Her postoperative course was characterized by pains in the lower extremities, a severe colicky pain in her abdomen, and a "constricting" pain in her chest. She vomited, was depressed, and suffered from insomnia. Her abdominal wall was rigid, and she had cramp-like pains in her abdomen. It was observed that her complaints were "entirely similar to those preoperatively even though she is minus an appendix." Her wound healed well. She was discharged on April 29 although she was still complaining of fleeting abdominal pains.

On admission, her urine was brown in color and showed a trace of sugar but was otherwise within normal limits. Her blood cell count showed 4,000,000 erythrocytes and 9,000 leucocytes per cubic millimeter; of these, 70% were neutrophiles and 30% were lymphocytes. Other specimens of urine were noted to be "red."

On April 26 no sickle cells were found.

This patient was again seen by one of us (G. A. S.) on May 13, 1945. She said that rather quickly some months before this she had developed a weakness of both of her upper extremities. Soon thereafter they became paralyzed. A few days after the onset of the weakness of her upper extremities, both of her lower extremities became weak and then paralyzed. She felt that the progress of her disease had been slow but definite. Her mother, however, felt that for a time she had not been so weak and had seemed to improve, only again to relapse. She had occasionally experienced a little difficulty in swallowing. She talked in a whisper, though quite clearly. She said she could talk louder but it was too much of an effort to do so. She had experienced no difficulty in controlling her urine, but she had some fecal incontinence.

The neurologic examination showed no change in the optic fundi. Her pupils reacted well to light and in accommodation-convergence. Her eyeballs moved fully. There was no nystagmus. The muscles of her face, tongue, jaws, and oropharynx moved fully. The patient enunciated well but talked in a whisper. There was some weakness and definite wasting of the sternocleidomastoid muscles and of the trapezii. The other cranial nerves were intact.

The patient had a quadriplegia. All her muscles were flaccid. There was marked wasting of all of the muscles of her extremities, chest, abdomen, and back (Fig. 1). She was barely able to lift her head off the pillow. There were no fasciculations. When the atrophied limb muscles were struck with a percussion hammer, a peculiar change was observed. The muscles, which seemed to be merely strands of fibrous tissue because of the vast wasting, would, briefly, slowly contract and slowly relax. This was not a local long-maintained myoedema, as seen in myotonic dystrophy or myxedema, for the contraction was not maintained and the contraction was just as slow as the relaxation.

Position sense and vibration sense seemed to be intact throughout. Touch sensation was lost distally in the lower extremities. It was impaired in the proximal portions of the lower extremi-

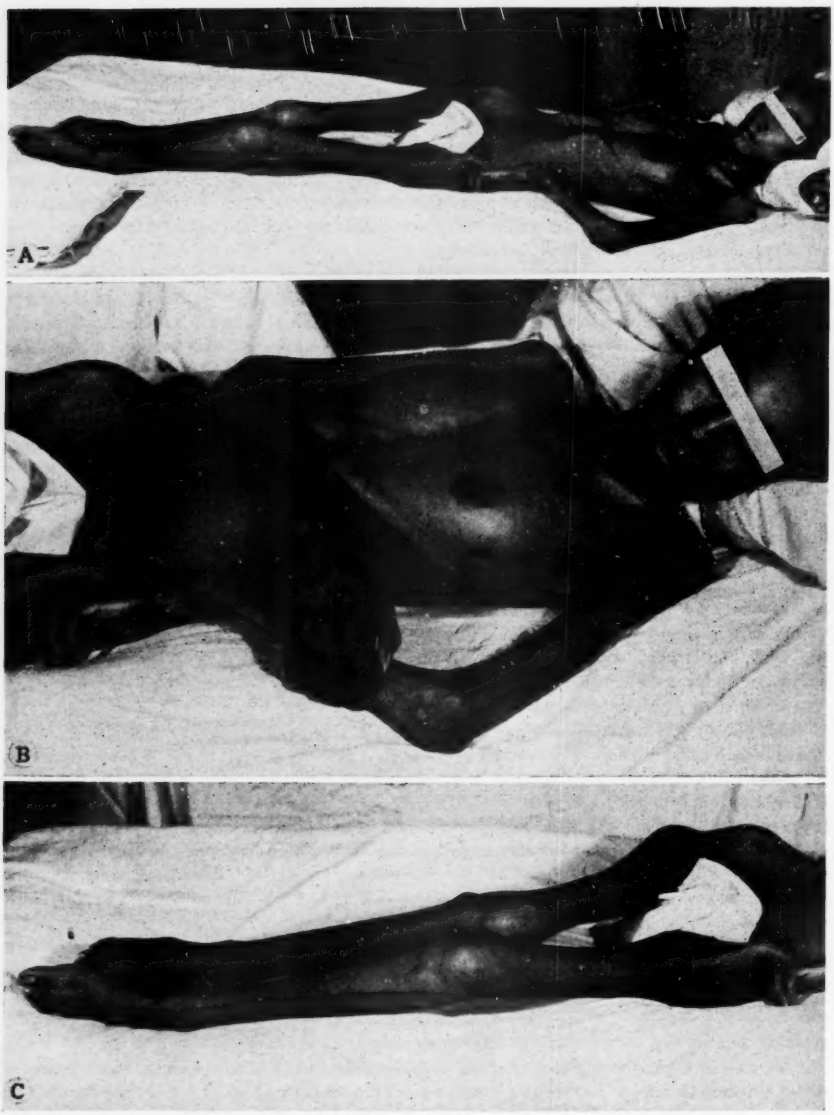

Fig. 1 (Case 2).—Photographs taken in May, 1945, several months before death. The extent and intensity of the atrophy of the muscles of the trunk and extremities are clearly evident in these pictures.

ties, in the abdomen, in the chest, and in the distal portions of the upper extremities. Touch was best perceived in the neck, head, and face. Pain perception was more extensively involved. Analgesia was evident in the lower extremities, but this faded out to a hypalgesia in the proximal portions of the lower extremities and in the body. Above the level of C-3 or C-4 pain was perceived normally. There was greater disturbance of pain perception in the lower extremities than in the upper extremities, but in all the limbs the disturbance was greater distally. Temperature sense was not lost, although it was markedly impaired, again, more distally in all extremities but more so in the lower than in the upper extremities.

The jaw reflexes were present but hypoactive. The pectoral reflexes were obtained, but the response was slower than normal. All of the other tendon, periosteal, and cutaneous reflexes were absent. There were no pathologic reflexes.

The patient died in 1945. No necropsy was permitted.

CASE 3.—H. K., a white unmarried woman, was 24 years old at the time of her death, on Nov. 28, 1946.

In March, 1945, this young woman, then a member of the WAVES, had her first attack of abdominal pain and vomiting. She was hospitalized because of recurrences of these symptoms, and a diagnosis of "gastritis" was said to have been made at this time. She was also found to have a vascular hypertension for the first time. She was given a medical discharge from the service in March, 1946.

She was admitted to Sacred Heart Hospital, Allentown, Pa., on April 6. At that time she complained of severe intermittent generalized abdominal pain of two weeks' duration. This was localized chiefly in the area about the umbilicus and epigastrium. She had been vomiting for 10 days and had complained of constipation for 6 days prior to admission. The abdominal pains were unrelated to meals and were unrelieved by any oral medication. The examination on admission revealed a tenderness to palpation of the epigastrium, periumbilical area, and right upper abdominal quadrant. There was no spasm of abdominal muscles.

Laboratory Studies.—Several urine specimens were of usual color and showed a few leucocytes and albumin. The blood cell count on admission was 4,000,000 erythrocytes per cubic millimeter; hemoglobin was 85%, and there were 7,400 leucocytes per cubic millimeter, of which 76% were polymorphonuclear leucocytes and 24% were lymphocytes. The blood Kolmer, Kahn, and Mazzini tests were negative. The blood type was II A. A Friedman test was negative. Blood urea nitrogen was 15 mg. per 100 cc. A lumbar puncture on April 24 showed a pressure of 25 mm. of mercury (325 mm. of water). The cerebrospinal fluid was clear and contained 31 cells per cubic millimeter; the protein was 27 mg., the sugar was 89 mg., and the chlorides were 640 mg. per 100 cc.; the Wassermann test was negative, and the colloidal gold test read 4444433210. A cholecystogram on April 18 revealed a "nonfunctioning" gall bladder but no stones. On April 24 a skull roentgenogram showed nothing unusual.

On April 9 a laparotomy was performed under thiopental (Pentothal) sodium and nitrous oxide anesthesia. The under surface of the gall bladder was bound with adhesions, and it was removed, as was the appendix. The postoperative course was characterized by a prolonged low-grade febrile response and a blood pressure which varied irregularly between 120/90 and 170/130.

The microscopic studies showed the gall bladder mucosa to be hyperplastic and fibrotic and to contain scattered foci of inflammation. These changes were thought to allow a diagnosis of cholecystitis. The appendix was thickened and showed fibrous and fatty infiltration.

Hospital Course.—On the second postoperative day (April 11), the patient began to complain of pain in the region of her incision and generally in her abdomen. These complaints continued intermittently until the 15th postoperative day.

On her sixth postoperative day (April 15), about 6:30 a. m., the patient had a "convulsion." The nurse described events as follows: "Slight frothing of mouth, kicking feet and swinging arms wildly, throwing off nightgown and bed clothes, snatching at incision. Pupils dilated and patient did not respond." This is said to have lasted 15 minutes. Also later in this day she complained of "feeling afraid," but no further details were available.

On the seventh postoperative day (April 16), at 5:30 a. m., she had a similar episode, during which she was somewhat cyanotic. This episode lasted five minutes and recurred twice within the ensuing hour. Twitchings of the upper and lower extremities, face, and head were observed.

About 8 p. m. on this day, she had another attack of twitching of her head and eyelids, but there was no cyanosis. She was restless afterward. Another attack occurred at 11:45 p. m. that day. She was generally restless and anxious until her 14th postoperative day (April 20).

On April 19 she was started on penicillin, 20,000 units every three hours intramuscularly. This was continued through April 26. By April 22, it was evident that the patient was better, and by April 26 her temperature became normal and she was thereafter asymptomatic. She was discharged on May 7.

The patient was readmitted to the Sacred Heart Hospital, Allentown, Pa., on Nov. 3 (service of Dr. L. W. DiLeo). The patient had begun to have abdominal pain, nausea, and vomiting about five weeks before the readmission. The pain had persisted and had become much more severe several days before she reentered the hospital.

On this admission, her blood pressure was 170/120. There was generalized abdominal tenderness, especially in the umbilical region. Laboratory studies showed a urine which was "port wine" colored and contained a trace of sugar. Tests of the blood for syphilis were again negative. The blood urea nitrogen was 16.4 mg., and the blood sugar was 139 mg. per 100 cc. The blood studies revealed a hemoglobin of 85% and 4,300,000 erythrocytes and 5,000 leucocytes per cubic millimeter, of which 65% were polymorphonuclear leucocytes and 35% were lymphocytes. Several other urinalyses showed a "port wine" or "red amber" color, an acid reaction, a specific gravity of 1.018 to 1.030, once a trace of sugar, albumin, 5 to 35 erythrocytes per high-power field and often many leucocytes.

An intravenous urogram suggested poor concentration of the dye, but the study was unsatisfactory because of the large amount of gas in the intestines. A gastrointestinal series on Nov. 8 revealed no abnormality of the stomach, duodenal cap, or small intestine. A barium enema on Nov. 12 showed the barium column to be stopped at the hepatic flexure.

On Nov. 7 one of us (G. A. S.) examined the patient neurologically and found slight swelling of the nasal borders of the optic nerve heads, an impairment of touch perception on the dorsum of the hands and feet, and a mild hyperalgesia of the dorsum of the feet.

On Nov. 13 an exploratory laparotomy under thiopental sodium and nitrous oxide anesthesia was performed. The omentum was observed to be adherent to the large intestine and the anterior abdominal wall. A definite kink due to dense adhesions at the hepatic flexure was noted, although it was thought that the obstruction here was only partial.

Irrational talk was noted on the night following surgery. Abdominal pain recurred on the second postoperative day.

On Nov. 17 the patient was still vomiting occasionally, had abdominal pain, and was first observed to be weak. She also had pain in her legs and thighs. She thereafter had episodes of irrational and noisy behavior and became generally uncooperative.

The patient was admitted to the Hospital of the University of Pennsylvania, Philadelphia, on Nov. 21. On admission, her blood pressure was 170/130, pulse rate 110 per minute, respiratory rate 20 per minute, and temperature 98 F. Except for some small submaxillary nodes on each side and a tender node in the right axilla, the general examination revealed little of significance. Before examination the patient was confused, couldn't answer questions well, and said eight people were going to cut her with knives. An hour later, she was mentally clear, answered questions well, and stated she had "bad dreams" in which she saw people with knives. There was a marked generalized weakness and generalized muscle wasting. She was unable to bring her hands to her face or to lift her knees off the bed; yet all parts could be weakly moved. Her speech was effortful but clear. There was weakness of the left internal rectus muscle. The left upper eylid drooped slightly. Pain perception was impaired over her forehead, chin, left side of head, both forearms, thighs, and lateral aspects of legs. Temperature sense was impaired in both thighs and legs. Vibration sense was impaired over her tibiae, and position sense was impaired in both of her large toes. The deep reflexes were decreased in the upper extremities. The knee jerks were absent. The ankle jerks were present and equally active. The abdominal reflexes were absent. There were no pathologic reflexes.

A careful family history was obtained from the patient's parents. No evidence of this disease had been observed in other members of her family. The urine of the patient's mother, father, and brother were negative for porphobilinogen (Dr. James Walsh).

Laboratory Studies.—The urine, freshly voided, fluoresced a red-violet under ultraviolet light, and on standing it became a rusty reddish color with a heavy precipitate. Using Watson's technique, the spectroscopic examination of the urine revealed a maximum absorption band at 560 mμ, characteristic of porphobilinogen.† No urobilin or bilirubin was found in the urine. The hemoglobin was 90%. There were 4,800,000 erythrocytes and 11,600 leucocytes per cubic millimeter of blood, of which 84% were polymorphonuclear leucocytes, 2% were monocytes, and 14% were lymphocytes. The blood urea nitrogen was 18 mg. per 100 cc. Fasting blood sugar was 84 mg. per 100 cc. CO_2-combining power was 72 vol. %. The total serum protein was 6.6 gm. per 100 cc. Prothrombin activity was 85%. The direct van den Bergh test was delayed, and the indirect reaction was 1.4 mg. per 100 cc. The blood tests for syphilis were negative. The blood cholesterol was 255 mg. per 100 cc. The blood serum chlorides were 88.2 mEq. per liter; blood serum calcium was 9.6 mg. per 100 cc.; serum total base was 139.6 mEq. per liter. The sedimentation rate was 49 mm. in an hour. Liver studies showed a total serum bilirubin of 2.9 mg. and a prompt direct-reacting serum bilirubin of 0.8 mg. per 100 cc., a cephalin cholesterol flocculation of ± in 24 hours and 2+ in 48 hours, and a thymol turbidity reaction within normal limits. An EKG showed a simple tachycardia. On Nov. 22 the CSF was under a pressure of 250 mm. of water; on Nov. 23 it was 340 mm. of water, with 50 erythrocytes per cubic millimeter, protein 50 mg. per 100 cc., at 4+ Wassermann reaction, and a colloidal mastic reaction of 2555532100. Repetition of the syphilitic serologic tests later gave a Wasserman reaction of 1244 and a colloidal mastic test of 4442100000.

Course in Hospital.—The patient was bedridden, emaciated, and obviously very ill when admitted. On Nov. 22 she had 8 to 10 convulsions lasting about one to two minutes each and occurring every two or three minutes. These consisted of clonic jerking of the head, with a tendency to turn her head to the left. Her shoulder muscles contracted, but little movement was seen in the extremities. Her jaws were tightly clenched, and her eyelids would close. The thigh adductors were in a state of tonic contraction. As soon as the movements ceased, the patient responded each time. She rapidly became weaker. On Nov. 23 she had a right peripheral facial weakness and slight respiratory difficulty. By Nov. 25 bilateral facial weakness was well developed. On Nov. 26 her respirations became so weak that she was put in a Drinker respirator. Her mental state varied considerably. She was delirious and confused at times but relatively clear and lucid at other times. On Nov. 28 her temperature rose to 104 F. rectally, a heart rate of 140 per min. persisted, her right pupil dilated, weakness of both external recti was noted, and she became comatose. She was unable to breathe without the respirator. Her cardiac activity ceased, and she died on this day.

General Pathologic Findings.—The postmortem examination was performed 15 hours after death. The gross examination disclosed generalized cyanosis, a recently healed surgical abdominal incision, emaciation, muscular wasting of the extremities, a healed mitral valvulitis, passive congestion and edema of the lungs, a surgical absence of gall bladder and appendix, and hypertrophy of the thymus.

The microscopic studies revealed the following: The pulmonary alveoli contained hemorrhages, edema fluid, and occasional pigmented macrophages. The cells of the liver were shrunken and pigmented, while the portal spaces, sinusoids, and veins contained an excess of polymorpho-

† Dr. C. J. Watson furnished us with the following information concerning the urine of Patient H. K.: "We received a sample in August, 1947, from Dr. James Walsh, with the record that this had been collected in November, 1946, and had been in the ice box during the interval. The amount was 1,200 cc., and it was not stated whether this was a 24-hour sample. The entire sample contained 420 γ of coproporphyrin and 29.8 mg. of uroporphyrin. The latter was isolated in crystalline form and was a Waldenström type porphyrin, separating on the calcium carbonate column into uroporphyrin I and a small amount of Type III porphyrin with ester melting point 206 C. This corresponds with the porphyrin which we have previously isolated under these circumstances and have found it contains seven rather than eight carboxyl groups, as is true of the uroporphyrin itself. Despite the fact that the urine had stood for such a long time (it was a very dark brown color), it still gave a faint but definite porphobilinogen aldehyde reaction."

nuclear leucocytes. There was a yellowish dusty pigment throughout the tubular cells of the kidneys. It was thought that the striated musculature showed indistinct cross striations, suggesting an atrophy of this tissue. The thymus was believed to be hyperplastic.

Neuropathologic Findings.—The gross examination of the brain, cerebellum, brain stem, and spinal cord revealed nothing unusual.

The brain and spinal cord were fixed in formalin. Portions of the nervous system were embedded in celloidin. Sections were stained with hematoxylin and eosin, the Weil technique for myelin sheaths, phosphotungstic acid, toluidine blue, and thionine.

Spinal Cord: Throughout all the levels of the spinal cord, the myelin sheath stains revealed no evidence of demyelinization within the fasciculi. The spinal roots, ventral and dorsal, never showed demyelinization in either their intramedullary or extramedullary positions. The dura mater and piarachnoid of the cord were unchanged. The blood vessels on the surface of the spinal cord disclosed no particular abnormalities. The intrinsic vascular tree occasionally showed perivascular infiltration with a few lymphocytes, but this change was insignificant at this level of the neuraxis. The glial elements throughout the cord gave little indication of participation in the pathologic process.

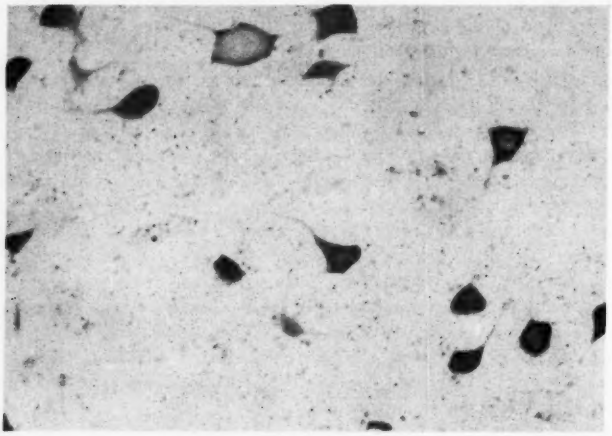

Fig. 2.—Cervical portion of spinal cord. Part of an anterior horn illustrates the variation and extent of neuronal changes. Toluidin blue stain; × 120.

The neurones were the elements which showed the most evidence of disease in the spinal cord. The greatest neuronal change was noted throughout the cervical portion. Here the somatic motor cells of the ventral horns were intensely involved (Fig. 2). There were few healthy, uninvolved neurones. The change occurred irregularly in severity and distribution, even within one anterior horn at any particular level. The degree of involvement was unequal on the two sides. In the midst of the devastated anterior horn cells, one would find several apparently healthy neurones. But the impression was that the smaller neurones were more likely to be preserved. The diseased cell bodies were rounded, swollen, and often markedly distended, like a balloon, with loss of their former multipolarity (Fig. 3*A*.) The nuclei were usually displaced toward the side of the cell bodies. The nuclei were deformed; often the nuclear membranes had disappeared. It was not unusual to find a naked nucleolus surrounded by a halo and displaced to one side of the cell body. The Nissl bodies disappeared, apparently at first about the nucleus, but finally the swollen cytoplasm of the neurones would stain a diffuse pale blue. Occasionally vacuolization of neurones was noted, and shrunken, sclerotic neurones were observed.

In the thoracic region, the anterior horn cells were fairly well preserved. Yet here and there one would find a sclerotic cell change or an early chromatolysis.

In the lumbosacral region the somatomotor nerve cells of the anterior horns showed the diffuse changes noted in such cells in the cervical region (Fig. 3*B*). But the process was far less severe and much less extensive at this lower level.

The cells of the dorsal gray matter and the small neurones of the substantia gelatinosa of Rolando showed no changes. The nerve cells of the dorsal nuclei of Clarke-Stilling were never

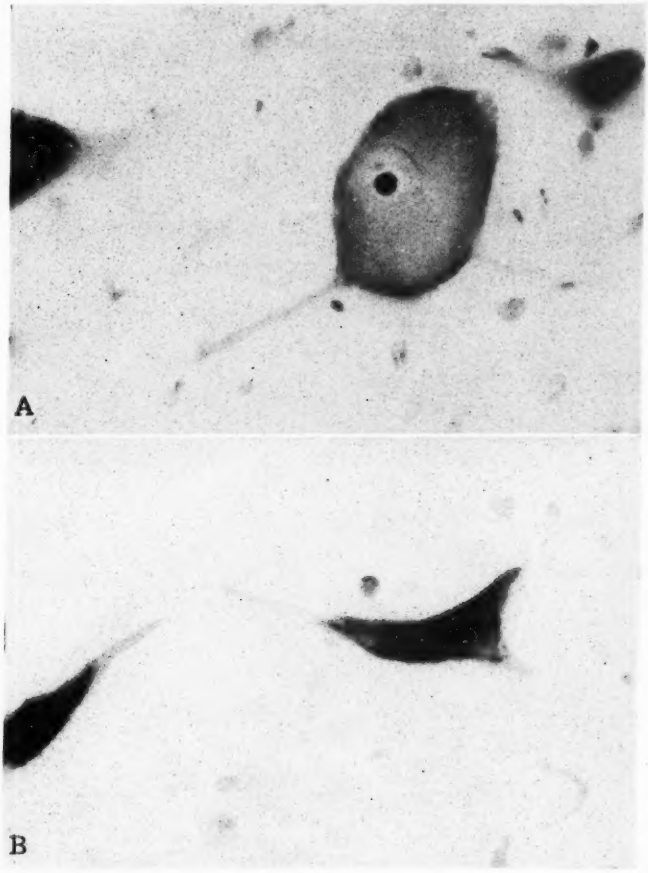

Fig. 3.—*A*, cervical portion of spinal cord. This anterior horn cell shows an intense swelling of its body. The Nissl bodies are destroyed, though a few granules remain at the periphery of the cell. The nucleus is shrunken, deformed, and displaced. Toluidin blue stain; × 512. *B*, lumbosacral portion of spinal cord. Neurones of anterior horn show sclerotic cell change. Toluidin blue stain; × 880.

changed. The splanchnic motor cells located in the lateral horns were for the most part unchanged, but here and there these cells too would be distended, with deformed and displaced nuclei and absence of Nissl material.

Medulla, Pons, and Mesencephalon: At no level were any significant changes noted in the piarachnoid or extramedullary blood vessels. The myelin stains revealed no evidence of demyelinization in these structures. Large vacuoles (so called corpora amylacea) were noted to be

scattered throughout, not more frequent in any particular area, not apparently related to the vascular system, but staining a homogeneous purplish blue with hematoxylin and eosin. No glial response other than swelling of the oligodendroglia was noted.

Even in the lowest levels of the medulla, one encountered vascular changes. Throughout the brain stem the changes about the blood vessels were perhaps the most striking pathologic feature. Changes were noted especially about the small and medium-sized vessels. The capillaries showed only swelling of their endothelium and occasional proliferation of these cells. The

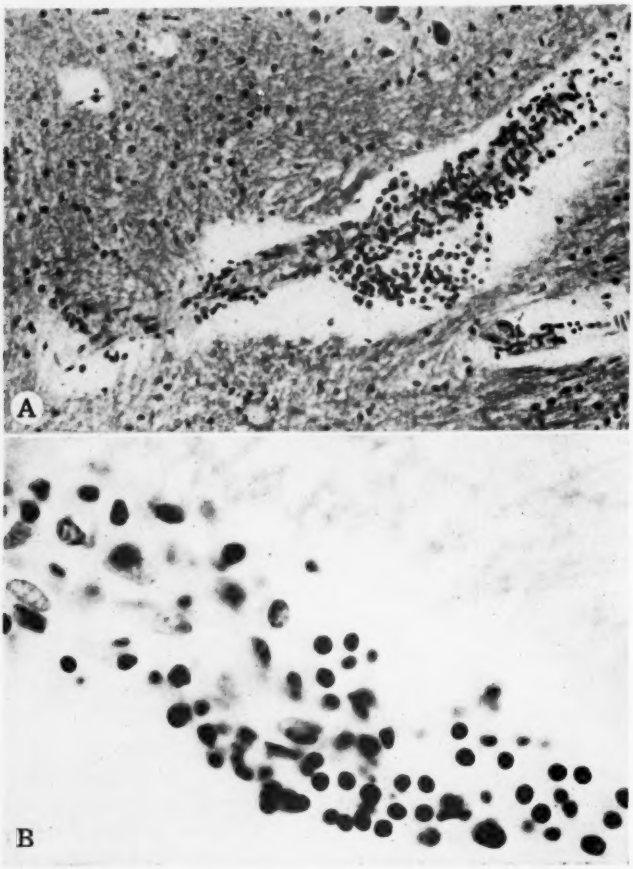

Fig. 4.—*A*, medulla oblongata. At the top, can be seen some of the neurones of the inferior olivary body. The blood vessel shows perivascular edema and perivascular cell infiltration. Hematoxylin and eosin stain; × 176; *B*, portion of the exudate of *A* to show the nature of the cells; plasma cells and lymphocytes can be readily identified. Note the swelling and increase in the endothelial cells of the vessel wall and the edema of the adjacent white matter. Hematoxylin and eosin stain; × 704.

other vessels showed perivascular edema, sometimes quite marked; perivascular infiltration with lymphocytes, occasional monocytes, and many plasma cells (Fig. 4), and a most striking plastering, stone-wall-like adherence of plasma cells to the vessel walls (Fig. 5). Along with these changes there seemed to be swelling and proliferation of the vascular cellular elements. Near the hypoglossal and dorsal motor vagal nuclei, petechial perivascular hemorrhages were

observed (a few also were observed at the level of the isthmus of the mesencephalon). In the upper pons, just caudal to the decussation of the trochlear nerve, the vascular changes seemed to be more marked nearer the aqueduct, and in the midbrain the periaqueductal gray matter definitely showed the most marked vascular changes.

The medulla. The neurones of the hypoglossal nucleus (XII) showed cell sclerosis, with Nissl masses clumped and linear and dendrites tortuous. A few of the larger cells of the dorsal motor vagal nuclei were sclerotic, and a few showed early chromatolytic change. The usual two

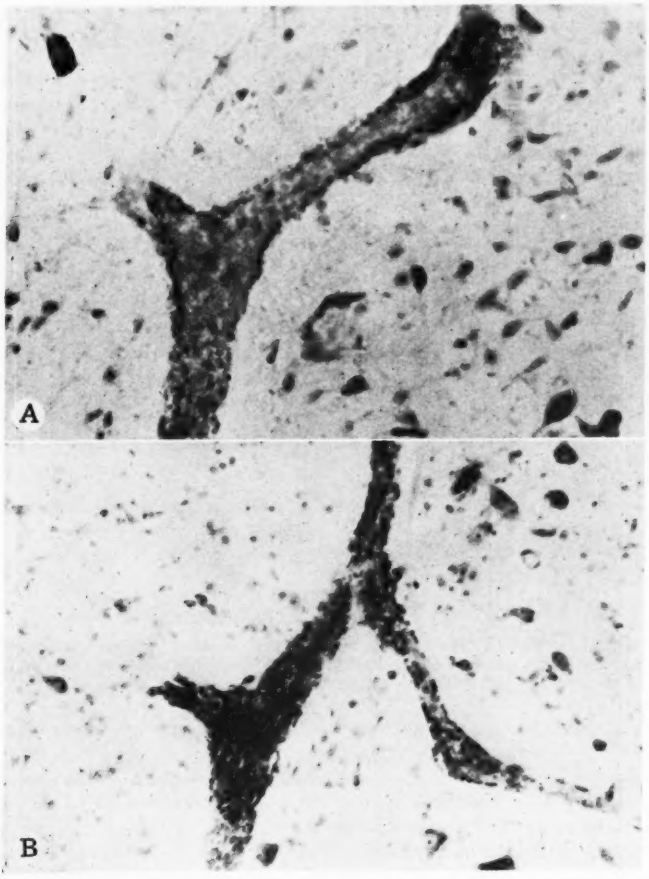

Fig. 5.—*A*, tegmentum of pons near locus caeruleus. The blood vessel shows the plastering of its walls with cells. Thionine stain; × 176. *B*, medulla oblongata near dorsal vagal nuclei. This blood vessel shows the intense collection of plasma cells and lymphocytes on its walls. Toluidin blue stain; × 176.

types of neurones of the nucleus gracilis and cuneatus were readily identified, but here too an occasional swollen, mildly chromatolytic change was noted. The neurones of the inferior olivary bodies showed mild changes. The motor neurones of the nucleus ambiguus (IX and X) showed infrequent, definite, but never severe chromatolysis. None of these neuronal changes were as severe or extensive as those seen in the spinal cord, although here and there one would encounter an obviously swollen cell with nucleus displaced and a pale blue cytoplasm resembling the bloated cells of the cervical cord.

The pons. Spotty cell sclerosis, pigmentary inclusion, and chromatolysis were observed in the neurones of the facial nerve (VII) (Fig. 6). The abducens nucleus (VI) contained neurones which seemed best preserved, for here there was only a very occasional cell sclerosis. The neurones of the pontine nuclei seemed intact.

The midbrain. The large motor neurones of the trochlear nerve (IV) on one side showed no change, but on the other side, where there was a group of severely involved blood vessels, the adjacent neurones showed early pathologic changes—fading out of the Nissl bodies, powdery material in the cytoplasm, nucleus displaced, and cell body swollen. Neurones of the nucleus paramedianus and of the mesencephalic nucleus of the trigeminal nerve (V) seemed to be intact. Here, as below, a very occasional neurone would show swelling and chromatolysis, but never the extensive severe change observed in the spinal cord.

Cerebellum: No abnormalities were noted in the piarachnoid. The myelin stains disclosed no areas of demyelinization, although here and there, with the perivascular edema, some thinning of the myelin was evident.

The changes in and about the blood vessels were again quite conspicuous. There were hypertrophy and hyperplasia of the cellular elements of the walls of the small vessels. Perivascular

Fig. 6.—Facial nucleus (VII). A portion of a healthy neurone is seen on the left; here the Nissl bodies are well defined, even in the dendrite at the top of the cell. The neurone on the right shows loss of the Nissl bodies and displacement of the nucleolus. Toluidin blue stain; × 480.

cuffing with plasma cells, lymphocytes, and occasional monocytes was again evident. Such changes were more prominent in the white matter.

The molecular layer showed no change. The cells of Purkinje presented minor and infrequent changes in the form of chromatolysis or cell sclerosis or nuclear shrinkage and displacement, while the granular layer was well preserved.

In the nucleus dentatus an occasional cell would show early chromatolysis. Almost all of the cells of this nucleus had a finely granular light-brown pigment in their cytoplasm. This material was clumped together in one area but did not occupy any consistent position within the cell bodies. A more frequent and conspicuous cellular change was the "ischemic-homogeneous" cell change—the Nissl material was granular and diffusely dispersed throughout the cytoplasm, with sometimes a halo free of the Nissl material about the nucleus; the nucleus was swollen, deformed, and stained so deeply that the nucleolus was often not discernible. There were areas where all the neurones were so affected, although this change was seen to occur irregularly and haphazardly throughout the nucleus (Fig. 7).

Diencephalon: This region was studied in sections taken at the caudal end of the putamen. No demyelinization was noted in the capsula extrema or the capsula externa. The neurones of the claustrum showed spotty changes. These were "ischemic-homogeneous" cell disease but were not so severe or so extensive as seen in the nerve cells of the nucleus dentatus. The puta-

men's small cells also showed spotty "ischemic-homogeneous" cell disease, but the large neurones seemed more severely affected. They were shrunken and deformed, with displaced, dense, distorted, and shrunken nuclei (Fig. 8*A*). The Nissl substance was a fine powder evenly spread throughout the cell body. In the putamen, the small cells in the medial portion of the nucleus near the globus pallidus showed similar changes; here, too, were the more severely damaged large neurones.

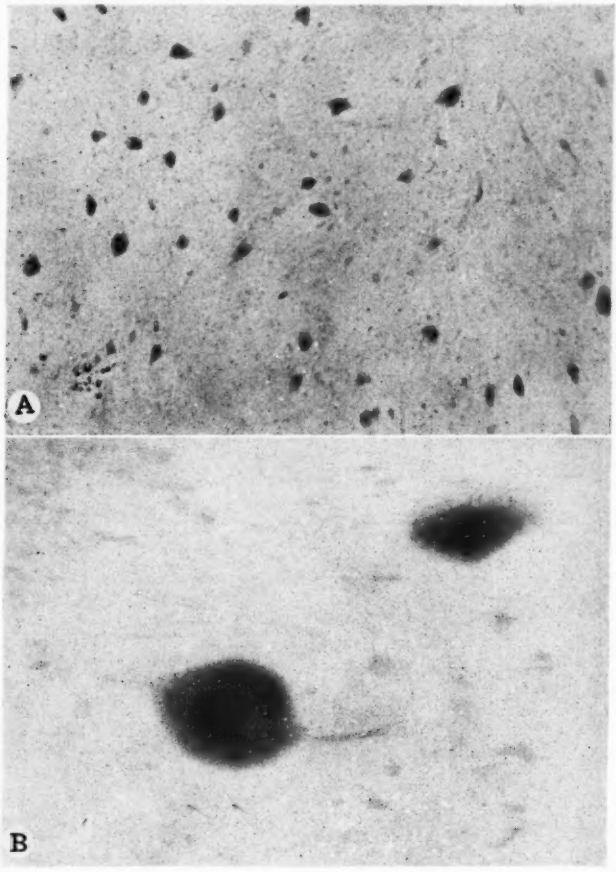

Fig. 7.—*A*, nucleus dentatus. Very few neurones of normal appearance are evident in this area. For the most part, dense deformed nuclei, swollen or deformed cell bodies, or shadowy cells constitute this damaged portion. Thionine stain; × 176. *B*, two neurones of the nucleus dentatus. The nerve cell at the upper right is shrunken and triangular in shape, while the larger cell is bloated. Both show a density of their nuclei and loss of Nissl material. Both contained pigment in their perikarya. Thionine stain; × 704.

The large cells of the caudal portion of the globus pallidus showed marked homogeneous cell change (Fig. 8*B*). The neurones were shrunken and deformed. The nuclei were dense, deformed, and displaced—often triangular in shape. The nucleoli were often not discernible but more frequently were displaced in the deformed nuclei. The Nissl material was dispersed as fine granular material throughout the cell bodies.

The small and large nerve cells of the tail and body of the caudate nucleus showed occasional changes, but these were thought not to be significant or marked.

No neuronal alterations were observed in the nucleus subthalamicus. Some of the unpigmented cells of the zona reticulata of the substantia nigra showed chromatolysis—swelling of perikarya and loss of Nissl bodies.

The nucleus anteroventralis thalami, nucleus mediani thalami, nucleus medialis thalami, and the nucleus centri mediani thalami showed no significant cellular changes. However, the

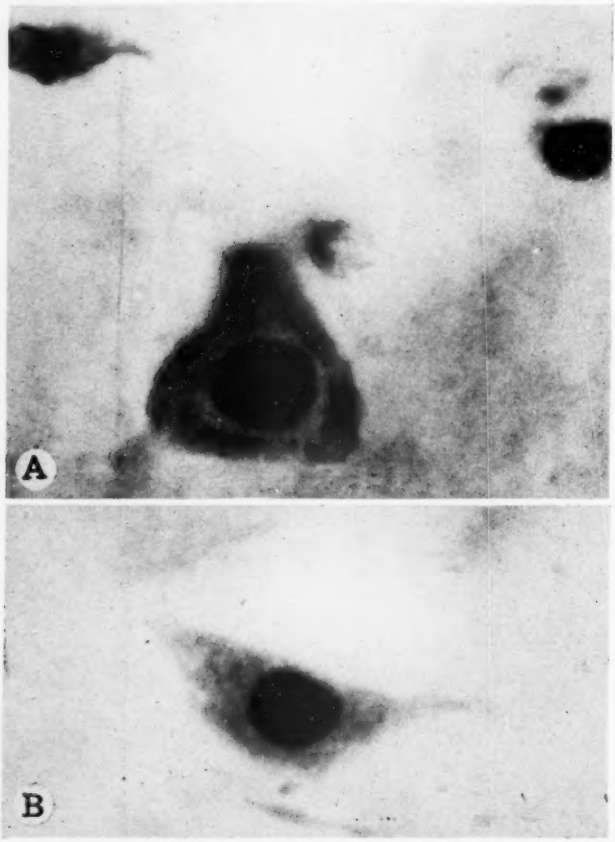

Fig. 8.—*A*, putamen. One large neurone and two small neurones are shown. All show "ischemic-homogeneous" cell change. The large cell of the putamen particularly illustrates the moderate degree of this change. Note the dense, irregular nucleus, the perinuclear halo, and the foamy cytoplasm, with Nissl bodies still persisting at the cell periphery. Toluidin blue stain; × 1,360. *B*, caudal portion of globus pallidus. A large neurone showing intense homogeneous cell disease. The neurone is triangular in shape; all the Nissl bodies have been lost; the nucleus is irregular in shape and stains very darkly. Toluidin blue stain; × 640.

neurones of the nucleus reticularis thalami showed marked abnormalities (Fig. 9*A*). The cell bodies had lost their processes. The neurones were often triangular in shape. Their cytoplasm was deficient in Nissl substance, with often a clear, unstained perinuclear halo of pallor. The nuclei were shrunken and deformed, with nucleoli often indistinguishable. In the nucleus lateralis thalami the nerve cells were for the most part well preserved, although neurones bordering on the

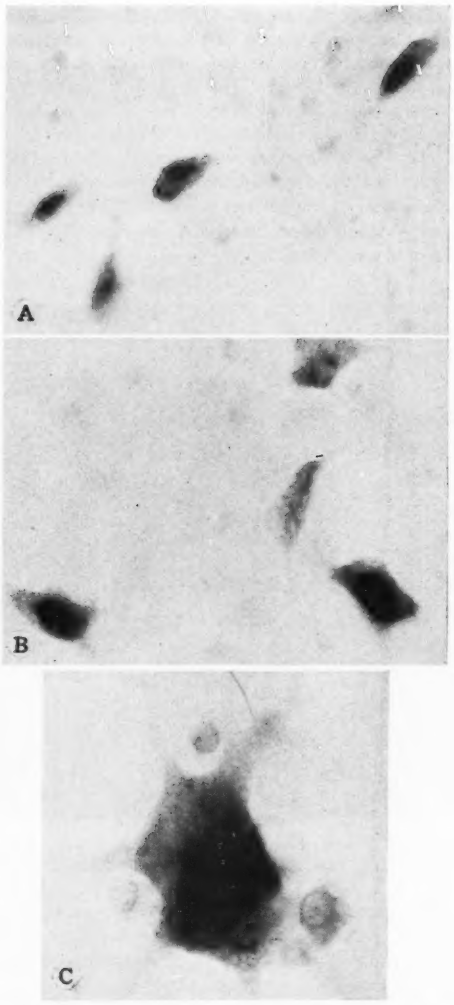

Fig. 9.—*A*, neurones of the nucleus reticularis thalami. Note the deformity and condensation of the nuclei. The cell bodies are narrowed and have lost their processes. The Nissl material is dispersed. Toluidin blue stain; × 907. *B*, neurones of the nucleus lateralis ventralis thalami. Two of the neurones show the "ischemic-homogeneous" cell disease seen so abundantly in this area. Toluidin blue stain; × 427. *C*, single neurone of the nucleus lateralis ventralis thalami. This shows in more detail the intense nuclear and cytoplasmic changes so often encountered in the nerve cells in some areas of the diencephalon. At the upper part of the cell body was a cluster of light brown pigment granules. Toluidin blue stain; × 907.

lamina medullaris lateralis thalami showed changes similar to those seen in the thalamic reticular nucleus. As one approached nearer to the nucleus lateralis ventralis thalami, more and more abnormalities were apparent in the nerve cells. Also, in the ventral portion of this nucleus, the neurones, diseased or not, contained a collection of granular yellow-brown intracytoplasmic pigment. The pathologic change in the neurones was again the "ischemic-homogeneous" cell disease. The most marked changes were noted in the neurones of the nucleus lateralis ventralis thalami (Fig. 9*B* and *C*). The greatest change here was in the cells of the ventral and lateral portion of this nucleus. Most of the cells of the nucleus lateralis ventralis thalami contained a large single collection of yellow-brown finely granular pigment in their perikarya. Some cells resembled those seen in the cervical cord—swollen bodies, Nissl material merely a fine blue powder, nucleus displaced, nuclear membrane lost, and so forth—but the changes were never so severe as in the anterior horn cells. More frequent was the "ischemic-homogeneous" cell change—nucleus dense, contracted, deformed, displaced; nucleolus not seen; cell body deformed, often triangular in shape; Nissl material powdery. Few healthy neu-

Fig. 10.—Surface level of a sulcus in the right parietal lobule. The swelling and cellular infiltration of the piarachnoid are readily apparent. Hematoxylin and eosin stain; × 58.

rones were noted in this nucleus, and in some areas every neurone was damaged. The nerve cells of the nucleus ventralis posteromedialis thalami showed the cytoplasmic pigment inclusions but only minor infrequent cellular changes, such as vacuolization or cellular swelling.

The neurones of the zona incerta and the nucleus ruber showed no consistent or marked change. Occasional cell sclerosis was noted in the neurones of the nucleus parvocellularis (parasympathicus) nervi oculomotorii.

Cerebral Cortex: Sections were available from major areas, and all showed the following changes: Throughout, but of course varying considerably in degree of involvement from one region to the next, was a marked change in the piarachnoid. These membranes were swollen, and in some places the constituent cellular elements were hyperplastic. The subarachnoid space contained a cellular exudate whose composition varied somewhat, often containing well-preserved erythrocytes and always composed of plasma cells, lymphocytes, and monocytes. While in general the exudate was well preserved, occasionally it was noted to be necrotic. The collections of exudate were most prominent about the blood vessels lying at the surface of the sulci (Fig. 10).

The vascular system presented a variable but consistent involvement in all cortical areas. The vessels of the piarachnoid showed little change other than marked edema of the cells of the walls of the small and medium-sized vessels. The arteries showed no change in their structure. Some veins at times showed an infiltration of cells in their walls, but this was not marked

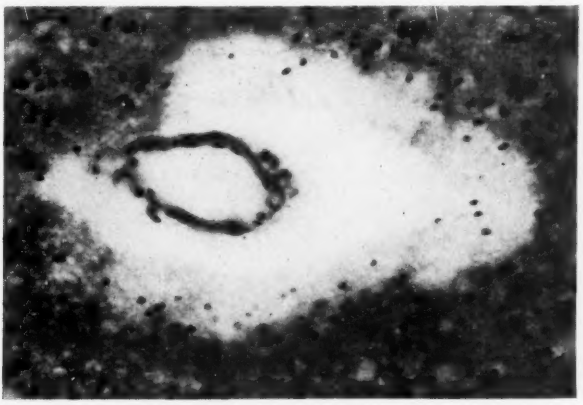

Fig. 11.—White matter in right frontal lobe. Note the marked perivascular edema with loss of staining quality of the adjacent white substance. Swelling of the cell bodies of the oligodendroglia is also apparent. Hematoxylin and eosin stain; × 270.

Fig. 12.—Pyramidal cells in lamina III of the fusiform gyrus. The neurones show swelling of the cytoplasm, with granular Nissl material clustered at the periphery of the cell bodies and about the nuclei—edematous cell change. Toluidin blue stain; × 448.

or definite. The vessels of the cortical gray matter showed edema of their walls, perivascular edema, and perivascular cuffing with plasma cells and lymphocytes, and in some sections of the frontal associational area there seemed to be occasional premortem thrombi in the small vessels.

The vessels of the white matter showed perivascular edema, perivascular infiltration with lymphocytes and plasma cells and monocytes, perivascular demyelinization, swelling and hyperplasia of the cells of the vessel walls, and hyaline-like swelling of the walls of the arterioles (Fig. 11).

The neuronal picture was well preserved in the inferior parietal gyrus, the island of Reil, and the superior temporal gyrus. In the gyrus dentatus, the cornu Ammonis, the gyrus hippocampus, and the gyrus fusiformis the nerve cells were also well preserved for the most part.

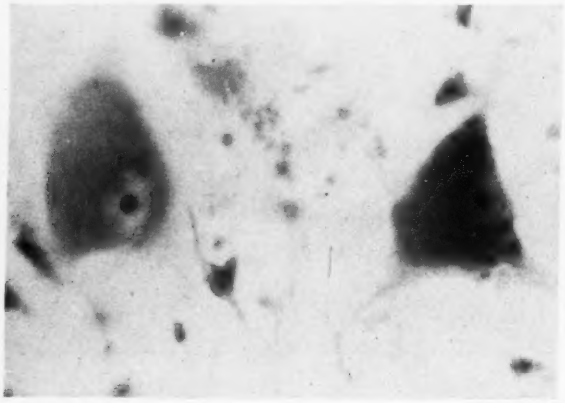

Fig. 13.—Giant cells of Betz in lamina V of the motor cortex. Both neurones are diseased—cell bodies swollen, nuclei displaced, tigroid bodies disintegrated. Thionine stain; × 420.

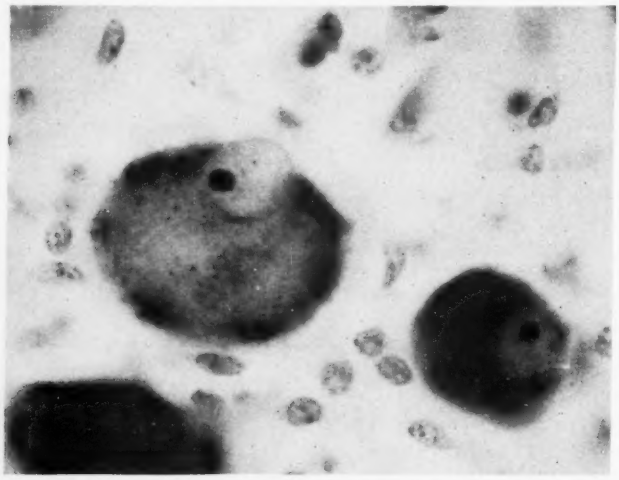

Fig. 14.—Neurones from autonomic ganglion of thoracic trunk. The large neurone in the center shows chromatolysis, nucleus displaced and almost extruded, nucleolus displaced, and pigment in its cytoplasm. Toluidin blue stain; × 850.

A few neurones in the cornu Ammonis showed pallor and loss of Nissl material. In the depth of the collateral fissure, the neurones of laminae II and III of both the hippocampal gyrus and the fusiform gyrus showed edematous cell change (Fig. 12*A*). This same change was observed in sections of the left temporal cortex, where neurones in laminae II, III and IV were involved.

Throughout all cortical sections some abnormal neurones could be found—"ghost cell" formation, homogeneous cell change, cell sclerosis, or chromatolysis. In no areas was the cyto-

architectonic pattern obviously disturbed. However, in the sensorimotor cortex more definite cellular changes were observed. Some of the large pyramidal cells of lamina III showed loss of Nissl substance, with the cytoplasm, pale and swollen, sometimes giving almost a "ghost cell" appearance. Occasionally, a "homogeneous-ischemic" cell change was noted in these neurones. Similar changes were noted in the large pyramidal cells of lamina V and in the pyramidal and fusiform cells of lamina VI. However, the most marked change was noted in the giant cells of Betz in the fifth layer (Fig. 12*B*). Often healthy Betz cells were observed, but the majority of these neurones showed changes which varied considerably in severity. The most severe effect was a swelling of the cell body, displacement of the nucleus and nucleolus, and disintegration of the Nissl bodies, with the cytoplasm staining a diffuse pale blue. A globule of granular brown pigment was often noted in these cell bodies. Occasionally, a Betz cell was seen with no Nissl substance and with a shrunken condensed deeply-staining nucleus.

The myelin stains never disclosed any abnormality other than the perivascular demyelinization.

Peripheral Nervous System.—We had available a portion of one femoral nerve, of the left tibial nerve, and of the left cervical plexus. The myelin preparation did not show any diffuse destructive change. There were a few swollen fibers, and in some areas it might be said that the myelin was "thinned," but nowhere could one find definite evidence of demyelinization. The supportive tissue between the nerve fibers showed no abnormalities.

Autonomic Nervous System.—Sections of ganglia from the celiac plexus, thoracic autonomic cord, and cervical autonomic chain were studied. The neurones in all these areas showed changes. The greatest changes were noted in the thoracic ganglia, but the changes were variable in the different areas. The neuronal changes were of two kinds: (1) edematous cell change and (2) chromatolysis (Fig. 13). The latter change was most frequent and varied considerably in degree within a single ganglion. The least alteration consisted of an increased density of the nucleus, with the nucleolus displaced within the nucleus and the nucleus displaced toward the periphery of the cell body; more marked change consisted of condensation of the nucleus, the nucleolus displaced, the nucleus at the periphery of the cell body or even extruding from the cell body, the loss of Nissl material at the center of the cell with remnants remaining at the periphery, and the collection of a granular yellow-brown pigment in the swollen cytoplasm. Occasional binucleate neurones were seen. The interneuronal tissues showed no changes.

COMMENT

Clinical Considerations.—The union of four pyrrole groups forms a porphyrin.‡ For instance, the union of four pyrrole groups with iron forms the porphyrin known as "heme." Further combinations of the iron porphyrin, heme, eventually produces the molecule known as hemoglobin.§ Some other porphyrin-containing molecules are myoglobin, cytochrome, catalase, and peroxidase. Apparently the body is able to synthesize pyrrole, and hence porphyrins, from relatively simple and abundant chemical substances.‖

Of all the theoretically possible porphyrins only Types I and III seem to have any biologic importance. Of these, coproporphyrin I and III and uroporphyrin I and III are normally excreted in the feces and urine of human beings.[6] For instance, coproporphyrin I is said to be excreted in the urine of a normal adult in quantities up to 150 γ per 24 hours, the others in only traces.[3] The urinary excretion of coproporphyrin I may be altered (increased or decreased) in certain blood[7] or liver diseases.¶ In some pathologic conditions,# Type III porphyrins begin to be excreted

‡ References 1-3.

§ References 1-3.

‖ References 4 and 5.

¶ References 8 and 9.

References 10 and 11.

in the urine; for instance, poisoning with some heavy metals, or with certain barbiturates, or with sulfonamides [12] may produce a porphyrinuria of this type.

However, there seem to be certain rare persons who are born with a defect in the metabolism of the respiratory pigments. This is evidenced by the appearance of increased quantities of the usual porphyrin isomers in the urine and feces. It is the presence of uroporphyrin in the urine which is said to be characteristic of porphyria. At times a colorless urine may be noted in acute porphyria. It contains porphobilinogen,[13] which can be converted to uroporphyrin by heating with a mineral acid. Obviously this must be a chronic metabolic defect. Yet sometimes the abnormal biochemical process seems to occur intermittently over long periods of time. Associated with the abnormal porphyrinuria are various clinical manifestations. Possibly depending somewhat on the isomers excreted, but depending more on the course of the disease, the clinical manifestations of porphyria have usually been classified as follows:

1. Congenital porphyria.[14] Recessive inheritance; males more commonly afflicted, in a ratio of 2:1; noted in infancy; continuous urinary excretion of uroporphyrin I and coproporphyrin I; syndrome consisting of cutaneous photosensitivity (hydroa aestivale), red-brown to purple pigmentation of teeth (erythrodontia), red urine, hirsutism, and bones discolored by uroporphyrin I.

2. Acute (intermittent) porphyria.[15] Dominant inheritance; females more commonly afflicted, in a ratio of 4:1; occurs in third and fourth decades of life; urinary excretion of uroporphyrin III and I, either predominating, with increased amounts of coproporphyrin III or I; large amounts of porphyrins excreted during the attacks; the colorless porphobilinogen (? precursor of porphyrin) may be found in urine; variably combined symptoms of (*a*) abdominal pain, vomiting, constipation, ileus, sometimes fever and leucocytosis and tachycardia, often vascular hypertension, (*b*) convulsions, sensory and motor disturbances of extremities, bulbar palsy, stupor, coma, death by respiratory failure, and (*c*) hypochondriacal complaints, restlessness, delirium, confusion, acute hallucinosis, and depression.

3. Chronic (mixed) porphyria.[16] A chronic disease, often considered to be a mild combination of the first two forms; continuous urinary excretion of large amounts of coproporphyrin III, but also coproporphyrin I, and uroporphyrin I and III. There is moderate cutaneous photosensitivity, abdominal pain, nausea, and vomiting.

Our cases represent relatively classic examples of the so-called acute, or intermittent, porphyria. It is this form which is of special interest to the neuropsychiatrist. The onset of this disease process, with acute abdominal symptoms (pain, nausea, and vomiting), is almost invariable. Because of the not infrequent accompaniment of low-grade fever, leucocytosis, and tachycardia, it is not at all surprising how often surgical procedures are carried out on these patients—only to have the same abdominal pain continue afterward. One wonders whether the usual preoperative barbiturates, anesthetic agents, postoperative sedatives, or antibiotics might or might not aggravate the disease in a susceptible person.

Then a series of symptoms and signs may appear indicating involvement of the nervous system.[17] Apparently there is nothing pathognomonic about the neuropsychiatric manifestations. They vary considerably in severity and variety from case to case. The rapidity of development and the rate of progression of the symptoms also vary. Often the clinical picture is that of a severe polyneuritis,* which may develop quite gradually at times. The neurologic picture may be that of a progressive involvement of the spinal cord, as is described in the symptom-complex known as

* References 18-20.

Landry's ascending paralysis.[21] This may progress to involvement of the cranial nerve nuclei, with resultant bulbar palsy and death due to respiratory failure.† The neurologic picture may last a long time, with apparently complete recovery.‡ The process may manifest itself by progressive weakness and intense atrophy of voluntary muscles.§ Convulsive seizures occur not infrequently.‖ Symptoms may develop rapidly into a toxic delirious state, with hypersomnolence or coma.[29] Nuchal rigidity and Kernig signs,[29] pleocytosis, hyperalbuminosis, and increased pressure of the cerebrospinal fluid ¶ and porphyrins in the cerebrospinal fluid have been recorded.

Mental symptoms may develop very early. Anxiety attacks have preceded the development of neurologic symptoms.[30] The mental symptoms may be the most marked indication of the disease process,# although the etiologic importance of porphyria in psychiatric processes may have been overemphasized.[33] However, in some of the cases a chronic emotional disturbance may develop.* Or, what is more likely, a confusional, delirious, hallucinatory mental state may develop and extend into the stage of stupor and coma.

The mortality rate once the neurologic symptoms have developed has been estimated as over 75%, but apparently chronic invalidism and complete recovery can ensue. What factors determine the course of the illness are still unknown, but the use of certain drugs (barbiturates, heavy metals, sulphonamides, etc.) probably can accentuate the metabolic disorder.

The occurrence of acute porphyria in the Negro race is apparently rare.[30] We found only four reports describing this form of porphyria in Negroes, although congenital porphyria has been described in the Bantu natives of South America. The reason for this racial discrimination is presently obscure.

NEUROPATHOLOGIC CONSIDERATIONS

It has been stated that the pathologic changes in the nervous system in porphyria were "not marked" or were "disappointing." This is certainly contrary to our findings. Hence we reviewed the available literature † and obtained the following significant data on this phase of the subject.

It is certainly true that some patients with acute porphyria have presented severe neurologic symptoms and signs, yet careful studies of their brains, brain stems, spinal cords, and peripheral nerves have revealed nothing abnormal.‡ The lack of demonstrable findings in such cases may result from the rapidity of the disease process, or perhaps the effect may be at a biochemical, not anatomically demonstrable, level. Of special interest in this respect are observations made by ultraviolet microscopy [66]—the liver, kidneys, and costal cartilage were fluorescent and fluorescent droplets were scattered throughout the spinal cord, cerebellar cortex, cerebral cortex, and pituitary body.

† Case 1 in Reference 15 and Reference 22.
‡ References 18-20 and 23.
§ References 24 and 25.
‖ References 26-28.
¶ Case 1 in Reference 15 and Reference 29.
# References 31 and 32.
* Case 2 of Reference 18.
† References 21, 25, 28, 33, 34, and 37-65.
‡ References 15, 22, 34, 66, and 67.

However, a study of the reported pathologic findings (47 cases) suggested several patterns of effect in porphyria. In the first place, there seem to be some cases in which the pathologic process effects only (or chiefly) the peripheral nerves.§ There may be slight changes in the anterior horn cells in such cases, secondary to peripheral nerve involvement.‖ The pathologic changes described in the peripheral nerves are in no way pathognomonic of porphyria, being chiefly a patchy asymmetric Wallerian type of degeneration. Some changes have been believed to resemble those produced experimentally by ischemia.[56] Infiltrating cells and pigment have been noted in the demyelinated peripheral nerves.¶ The Schwann cells and the connective tissue elements have shown proliferative responses at times.# Of the 47 reports, the peripheral nerves were examined in 25 cases and in only 5 were they found to present no abnormality. Apparently, therefore, the peripheral nerves are quite vulnerable in porphyria and react to give the histopathologic picture seen in any toxic multiple neuritis.

The next pathologic pattern that seemed apparent from a study of the literature was the involvement of the neurones of the neuraxis. Of the 47 cases, the spinal cord was examined in 41. In 10 of them, no alterations were seen in the spinal gray or white matter. Indeed, in only 5 cases was there evidence of damage to the white matter of the spinal cord, but in 31 cases definite changes were noted in the neurones of the spinal cord. The neurones chiefly involved were the anterior horn cells. Occasionally, the neurones in Clarke's column, in the lateral horns, or in the posterior horns were reported to show changes. While the disease process was often noted diffusely throughout the cord, it was not unusual to have reported greater involvement at the lumbosacral or cervical levels. The neuronal changes occurring in the spinal cord were, again, not pathognomonic of porphyria—there were cytoplasmic pigmentation, cell sclerosis, severe neuronal disease, vacuolization and cell loss, but chiefly swelling of neurones and chromatolysis. Some authors believed that the anterior horn cell changes were secondary to the peripheral nerve changes.*

The brain stem was examined in 17 cases. In none were there definite changes in the white matter, while in 10 cases there were variable changes in the neurones of the somatomotor and visceromotor nuclei of the brain stem. The neuronal changes were essentially like those noted in the spinal cord but were usually less severe. Some variable vascular changes were reported in a few cases, but these findings were not consistent or marked.

The cerebellum was studied in 17 cases, with changes noted in 10. In these cases, the neurones of Purkinje and/or of the dentate nucleus were damaged.

The cerebrum was investigated in 27 cases. Significant changes were noted in 20 of these. The changes consisted of neuronal disease of varying types and degree in various cortical areas. Again, there was nothing to be considered here as peculiar to porphyria.

§ References 25, 39, 41, 43, and 51.

‖ References 46 and 58.

¶ References 12, 21, 46, 56, 61, 62, and 64.

References 48, 56, and 65.

* References 48, 52, and 63.

Throughout the spinal cord, brain stem, cerebellum, and cerebral hemispheres it would seem that porphyria chiefly affects neurones, most profoundly in the spinal cord but somewhat throughout the entire central nervous system. This is the picture encountered in a polioencephalomyelitis.

Of interest were the destructive changes noted in the spinal ganglia † and in the autonomic ganglia.‡ The former, along with the peripheral nerve changes, might well explain some of the pain, paraesthesiae, and other sensory disturbances encountered in these cases. In our third case, we noted changes in the neurones of the nucleus ventralis posterolateralis of the thalamus, which would indicate further sources of sensory disturbances in such patients. The involvement of the autonomic ganglia has been suggested as possibly one of the sources of the abdominal pain which dominates the early clinical events in porphyria. This too may explain the various other gastrointestinal and visceral symptoms so often noted in porphyric patients.

In some of the reports § changes were observed in the striated musculature. Further studies might be done to determine whether the muscle wasting of acute porphyria is primary or is secondary to the peripheral nerve involvement. The fact that myoglobin is formed by porphyrins might indicate a primary effect in the muscle itself in porphyria.

The neuropathologic findings in our third case indicated involvement of the following structures throughout the nervous system: the leptomeninx (piarachnoid), the intrinsic vascular system, and the neurones. The meningeal involvement was chiefly over the cerebral hemispheres. It consisted of swelling of the piarachnoid and an infiltration with red blood cells, lymphocytes, monocytes, and, particularly, plasma cells. The vascular system within the neuraxis showed the most marked changes in the brain stem and the least in the spinal cord. These changes were edematous, proliferative, and exudative. The most conspicuous and consistent vascular finding was the perivascular accumulations of plasma cells and lymphocytes. Possibly of more significance was the tremendous damage to the nerve cells. The neuronal changes were nonspecific cellular changes—edematous cell change, severe acute neuronal disease, chromatolysis, cell sclerosis, and, especially, the so-called "ischemic-homogenous" cell disease. The distribution of the lesions could not be considered as characteristic—the anterior horn cells, especially in the cervical portion of the spinal cord; various nuclei of the brain stem; the dentate nucleus of the cerebellum; the large neurones of part of the putamen and of the globus pallidus; the neurones of certain thalamic nuclei; the giant cells of Betz in the motor area of the cortex, and the neurones in the autonomic ganglia. The glia seemed to participate only in a passive way. The myelinated fibers showed insignificant alterations. There seemed to be little evidence in this study to relate the vascular with the neuronal changes, although here and there this was suggested. The total neuropathologic picture suggested a "toxic," rather than a "metabolic," effect. Hence, we felt this could rightfully be designated as a diffuse toxic meningopolioencephalomyelitis.

The neuropathologic findings in our first case also showed absence of change in the myelinated structures of the neuraxis and spinal roots. Essentially, pathologic

† References 41, 46, 56, and 60.

‡ References 46, 58, and 62.

§ References 25, 43, 51, 52, 55, 58, 59, and 64.

changes involved the leptomeninx and neurones. The vascular effects were pigmentation of blood vessel walls and perivascular hemorrhages. The cerebral subarachnoid space disclosed a picayune hemorrhage. The neurones of the cerebral cortex were particularly changed, suggesting "an acute toxic ganglion cell disease." There was less change noted in the neurones of the spinal cord. If survival of the patient had been longer, possibly more extensive neuropathologic effects would have occurred.

There still is considerable uncertainty as to just how the pathologic changes in the nervous system are produced in porphyria. Many investigators do not believe that it is due to the direct action of the porphyrins on the nervous system. Uroporphyrin and coproporphyrin have been identified in the cells of the nervous system.|| A patient taking hematoporphyrin (Photodyn) has been reported as having developed a polyneuritis.[70] Yet animals given large quantities of the porphyrins do not develop central nervous system disturbances.[71] Because of the frequent "minimal" findings at autopsy, a functional aspect of the disorder has been suggested; viz., the porphyrins may produce a chemical block in neuromuscular transmission.[22] It has been suggested that the effect is produced by the action on smooth muscle, for porphyrins do produce a spasm of smooth muscle, not always relieved by atropine. The spasm of smooth muscle by direct action of the porphyrins is said to account for abdominal pain and vascular hypertension. In the nervous system, such spasm of the smooth muscle of small vessels might produce an ischemia [56] and thus damage nerve cells. More recently, there has been a tendency to think that the presence of abnormal intermediate metabolites or an increase in the quantity of normal intermediate metabolites of porphyrin metabolism might be the factor involved, these acting directly on the cells.[71] From the available neuropathologic data and from a study of our cases, the direct cellular action of some toxic agent would seem to be the mode of production of nervous system symptoms in these cases of porphyria. Only future biochemical research will answer this question more accurately.

SUMMARY

The clinical and laboratory findings of three young women who suffered from acute (intermittent) porphyria are reported. Two of the three women were Negro sisters. All cases were fatal. Neuropathologic reports on two cases are recorded.

Our third case, studied neuropathologically, was found to show changes in the leptomeninges, in the intrinsic vascular structure of the neuraxis, and in the neurones of the autonomic ganglia as well as in those of the central nervous system. It was believed that these findings could best be explained as a diffuse toxic reaction—meningopolioencephalomyelitis.

A review of the available neuropathologic literature in porphyria seems to support such an assumption and indicates also that a multiple neuritis is commonly part of the neuropathologic effect in porphyria.

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ROENTGEN CHANGES OBSERVED IN GENERALIZED SCLERODERMA

Report of Sixty-Three Cases

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IN RECENT years considerable interest has been shown by many authors in the morphological changes in generalized scleroderma. Greater familiarity with the various pathological alterations has been achieved because of close observation and study of the necropsy material in postmortem examinations.

Pugh,[1] in 1948, gave a comprehensive review of the literature on the subject, with discussion of many of the pathological changes seen in the various body systems.

It is our objective to present a review of the findings seen in 63 cases of scleroderma observed in Duke Hospital during the past 20 years, with particular emphasis on the roentgen changes.

Table 1 shows the sex, race, and age incidence of this group of patients. In this series females outnumber males slightly more than 2:1. The majority of cases were in the 31 to 50 year age group (67%).

A review was made of the incidence and type of roentgenographic findings present in this group of cases. Not all of these cases included roengenographic studies, and in many the roentgenographic work was incomplete; however, 57 cases were collected which had one or more roentgenographic studies. The results of these studies are presented. Included in this study are those cases which were proved either by autopsy or surgical biopsy or by having sufficient follow-up so that a positive clinical diagnosis was made. Of the 57 cases which had one or more roentgen examinations, 45 cases had one or more of the changes which have been described by several authors * as occurring in scleroderma (Table 2).

RESULTS

For the purpose of presentation the positive roentgen findings have been divided into the following groups: findings involving gastrointestinal tract, bones and joints, soft tissues, and cardiovascular system and hepatic or splenic enlargement or both. We were impressed by the high incidence of positive roentgen findings in these systems (Table 3).

In this review no distinction was made among the various types of scleroderma, but the disease as a whole was considered as primarily one of abnormal collagen

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behavior. The collagen disorder may be associated with vascular abnormalities of wide range, such as Raynaud's phenomena, endarteritis, arteriolonecrosis, and, infrequently, periarteritis-like lesions, particularly in those vessels caught in the area of maximum collagen reaction. Although scleroderma may be considered a misnomer, because of the systemic generalization, it is interesting to note that 60 out of 63 cases had significant clinical evidence of soft tissue or vascular changes

TABLE 1.—*Sex, Race, and Age Incidence in Sixty-Three Cases of Scleroderma*

	Cases, No.
Male	20
Female	43
White	47
Negro	16
Age, Yr.	
0-10	0
11-20	3
21-30	3
31-40	20
41-50	23
51-60	8
61-70	6

TABLE 2.—*Incidence of Positive Roentgen Change**

	Cases, No.
Roentgen examination	57
No roentgen examination	6
Cases with one or more findings	45
Noncontributory cases	12

* 79% showed positive findings when examined.

TABLE 3.—*Incidence of Positive Roentgenographic Findings on Examination*

Part Examined	Total No.	No. Normal	No. Abnormal	% Positive
Lungs	54	29	24	44
Gastrointestinal tract	29	6	23	79
Bones	31	13	18	59
Soft tissues	31	4	27	87
Joints	31	14	17	54
Heart	54	32	22	40
Liver or spleen or both	24	11	13	54

in the hands. The roentgenographic examination is a good method of demonstrating the gross morphology of the pathological changes related to this disease process.

Lungs.—In 54 cases with chest roentgen studies it was found that the lung fields showed a pertinent abnormality in 24 cases (44%). The predominant change was found to be an interstitial-like infiltrative process in the central portions of both bases. This process tended to clear partially and then recur, with increased distribution upon each recurrence. As the disease progressed, the lung lesion became more widespread and a definite permanent, progressive fibrotic component became readily recognizable. In two cases large pneumonoceles were seen, with subsequent development of pneumothorax (Figs. 1, 2, and 3).

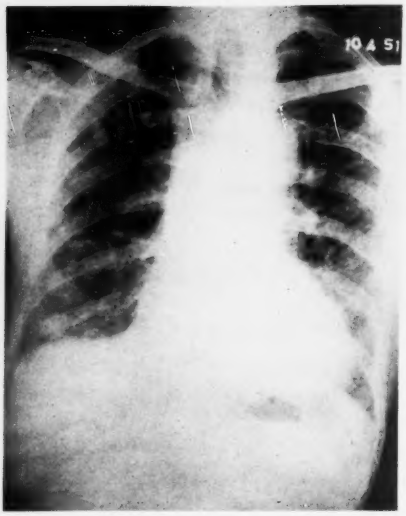

Fig. 1.—Focal fibrotic change throughout the lung fields. At autopsy, a year later, extensive pulmonary fibrosis was a noteworthy feature.

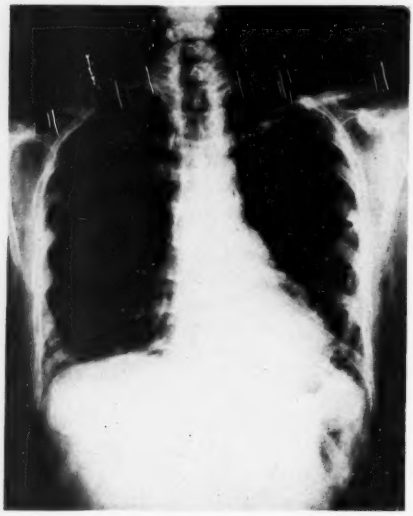

Fig. 2.—Basilar fibrosis and a large pneumonocele in the left base.

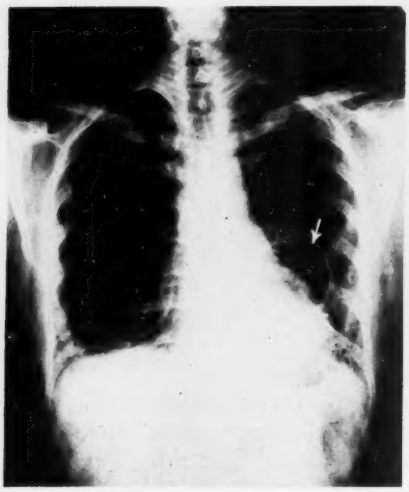

Fig. 3.—Same case as in Figure 2, with the cyst retouched. Shortly after this roentgenogram was taken the patient developed a spontaneous pneumothorax.

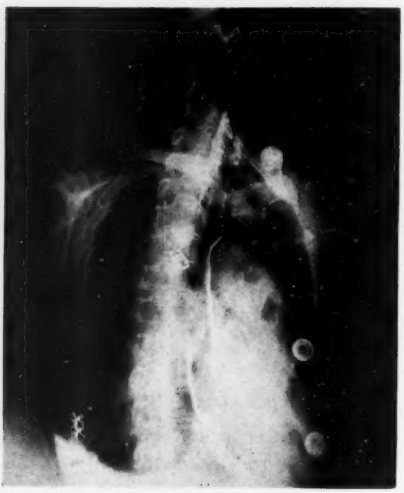

Fig. 4.—Thin-walled atonic esophagus. No perisaltic activity was present.

The necropsy findings in the lungs in cases of scleroderma are described in detail by Getzowa [3] and by Weiss and co-workers.[4] These changes consist of the presence of interstitial and alveolar wall collagen alteration, associated with endarteritis in some cases. There occurs disruption of alveolar structure as a result of collagen replacement of the elastic tissue in the walls of the alveoli. This leads to large cysts and blebs, predominantly at the periphery of the lung. Marked increase in collagen is present interstitially throughout areas of the lung in several cases, and endarteritis may or may not be seen. Fibrosis may be precipitated either by the vascular endarteritis or as a result of the collagen disorder following bronchiolar distribution.

Of the two necropsy cases studied, one was characterized by extensive fibrotic alteration and prominent vascular changes consisting of medial hypertrophy and intimal proliferation of the vessel walls. In the other, the appearance was similar to that described in the lung in so-called rheumatic pneumonia. Vascular changes were not a prominent feature in this case.

Gastrointestinal Tract.—Of 29 cases examined, 23 (79%) showed abnormality of the esophagus, and, whenever the stomach and small bowel were examined, abnormality in these organs was noted as accompanying the change in the esophagus as an associated finding.

The changes in the esophagus varied widely. They ranged from abnormality of transit time to markedly abnormal appearance. In some of the cases there was marked narrowing of the sphincter area, with dilation, loss of tone, absence of peristaltic activity, and marked retention of the barium. Some cases showed a generally narrow esophagus with rigid walls. The esophagus emptied only by gravity and showed absence of mucosal pattern. The precipitating factor for the changes in the esophagus is the collagen disorder and its affecting of the submucosal and muscular area. Degenerative muscle changes with thinning and atrophy occur. This may result in a dilated esophagus. The narrow rigid type is thought to be primarily caused by fibrosis, precipitated by repeated episodes of esophagitis. In one of the necropsy cases, in which there was esophageal change, there was a wide zone of collagen degeneration beneath the inner longitudinal layer of muscle. In the circular and outer longitudinal muscle layers there were seen changes of degeneration and regeneration of the muscle. The submucosal area showed considerable alteration of the connective tissue by collagen degeneration. No vascular changes were present.

Scleroderma of the stomach, small intestine, and colon has been reported much less frequently than esophageal involvement. In this study the stomach appeared flaccid, with marked delay in emptying. The four patients on whom small bowel examinations were done showed abnormality of segmental width and neuromuscular disturbance. Neuromuscular disturbance is of great importance as an explanation of the small bowel appearance. It has been reported that fibrosis may occur, producing narrowing of the small bowel (Figs. 4, 5, 6, 7, and 8). No abnormalities of the colon were recognized.

Bones.—The phalanges of the hand were examined in 31 cases. In 18 cases (59%) there were varying degrees of sclerodactyly, ranging from partial resorption of the ungual tuft of one phalanx to almost complete resorption of the terminal phalanges of all fingers of the hand. All these cases demonstrated one thing in common, that the resorption of bone originates from the distalmost point and progresses proximally.

Fig. 5.—Dilated esophagus with relative narrowing at the sphincter area. The stomach was noted to be atonic, and emptying was delayed.

Fig. 6.—A fairly rigid and narrow lower esophageal segment.

Fig. 7.—Dilatation of the small bowel thought to have resulted from neuromuscular abnormality.

Fig. 8.—Narrowing through sphincter area. The stomach was atonic, and neuromuscular disturbance was noted through the small bowel.

The cause for the bone resorption is not clearly established. In this group, sclerodactyly was present in the acrosclerotic fingers and in the swollen, enlarged fingers.

The skin and subcutaneous tissue in many cases show marked alteration, with wide range, as a result of the collagen disorder. Both endarteritis- and periarteritis-like lesions may be present. Raynaud's phenomenon was found in many of these cases.

Resorption of the bone was accompanied by acrosclerosis or by large swollen fingers in which severe vascular disturbances and marked proliferative changes were present, interfering with blood supply. It was not necessary to have acrosclerosis to see sclerodactyly; however, where there was progressive tissue atrophy, sclerodactyly was more frequently seen (Figs. 9 and 10). Clinical evidence and roentgen appearance point to the fact that the resorption of bone is caused by interference with blood supply to these parts.

Soft Tissues.—Roentgenograms of the hands were made in 31 cases. Twenty-seven cases (87%) showed a definite abnormality of the soft tissues. This consisted of swelling or atrophy of the part. In some cases there were calcium deposits. One of the early characteristic findings in the soft tissue was the multiplicity of linear changes of decreased density. The acrosclerotic fingers showed atrophy. In both types there were numbers of linear streaks of decreased density, much greater than that seen in the normal fingers. Neither the soft tissue changes nor the calcium deposits are necessarily confined to the fingers, since in several cases there was diffuse atrophy of shoulders and chest wall, with calcium deposits which were both subcutaneous and intramuscular. Much of the soft tissue appearance seen on film is similar to that seen in any severe peripheral vascular disturbance. Advanced proliferative soft tissue change was often present without any bone manifestation (Figs. 11, 12, 13, and 14). In this group it was noted that Raynaud's phenomenon was observed in approximately 50% of the cases with soft tissue changes.

Collagen disorders of the skin, subcutaneous tissues, and muscles account for these varied changes, as well as for the severe vascular disturbances which are frequently present. Calcium is deposited in areas of tissue necrosis. Obliteration of tissue planes by fibrosis is noted.

Changes may be proliferative or atrophic. Collagen swelling and necrosis, fibroblastic proliferation and fibrosis, and severe vascular disease may be present.

Joints.—There were 31 cases in which various joint examinations were done, and of this group 14 showed normal joints and 17 (54%) showed evidence of a rheumatoid-arthritis-like joint. The joints with positive changes included interphalangeal and carpal joints, elbow, shoulder, and knee joints and joints of the ankles and feet.

The joints showed atrophic changes due to synovial alteration as a result of the collagen disturbance of the synovia. The changes seen are similar to the changes ordinarily seen in any type of rheumatoid arthritis (Fig. 15).

Heart.—The group in which cardiac manifestations were recorded is possibly controversial to some extent. It was found that of 54 examinations of the chest 22 revealed an enlarged heart, which was believed to be related to the disease process, either primarily or secondarily (Figs. 16 and 17).

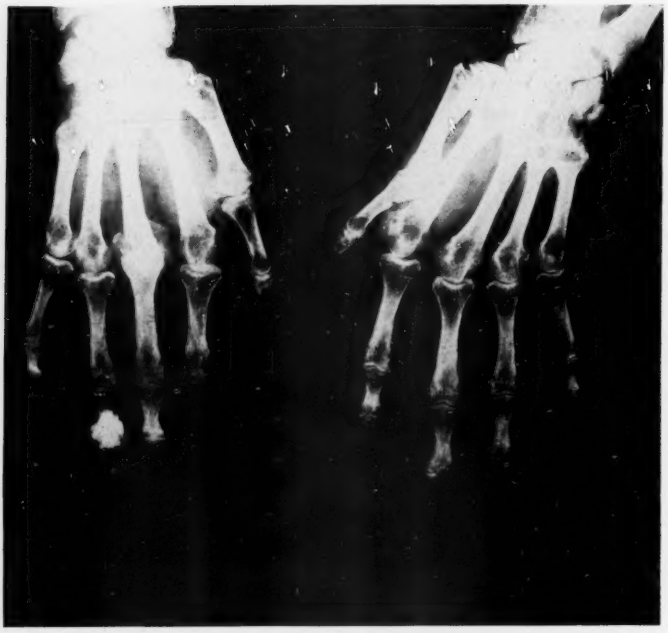

Fig. 9.—Acrosclerosis, sclerodactyly, and narrowed interphalangeal joints.

Fig. 10.—Sclerodactyly.

Fig. 11.—Thick fingers and multiple linear areas of decreased density.

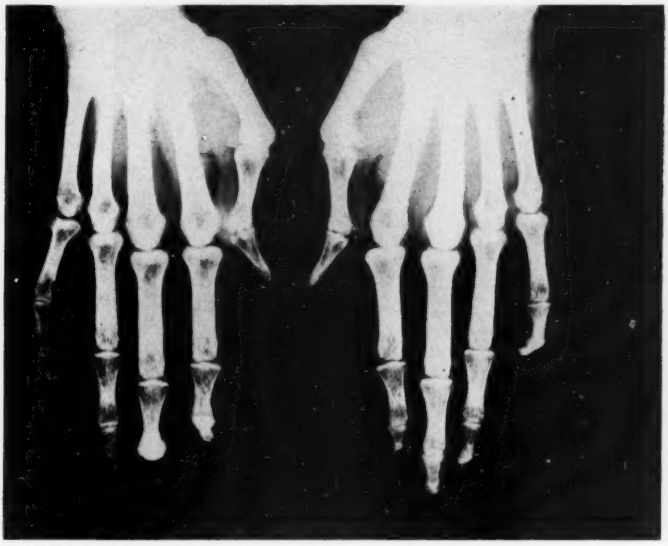

Fig. 12.—Acrosclerosis and sclerodactyly.

Fig. 13.—Calcium deposit intramuscularly about the shoulder.

Fig. 14.—Cervical spine, showing intramuscular and paravertebral ligament calcification.

Fig. 15.—Rheumatoid-arthritic-like change in the joints.

The electrocardiographic studies were varied. Both right and left axis deviation were present. Frequent conduction defects were noted. Bundle branch block was present in several cases.

Scleroderma of the heart was not well recognized until 1943, when Weiss and co-workers studied 9 cases with signs and symptoms of heart disease. They showed definite primary cardiac involvement by study of necropsy material. Focal scarring was the predominant finding to explain the primary cardiac change. Arteriolar disease was not a characteristic finding. In one of our necropsy cases the cause for myocardial disease was found to be many and numerous focal areas of fibrinoid degeneration of the myocardium. The patient died of heart failure which was in

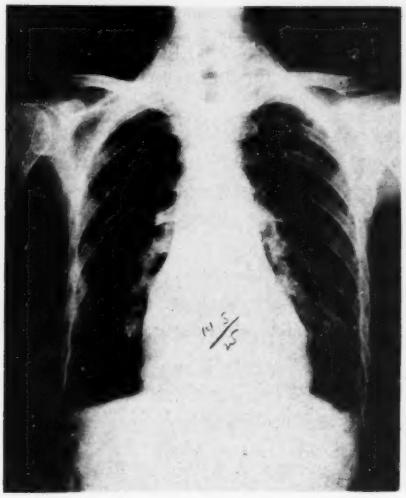

Fig. 16.—An enlarged heart through both salients.

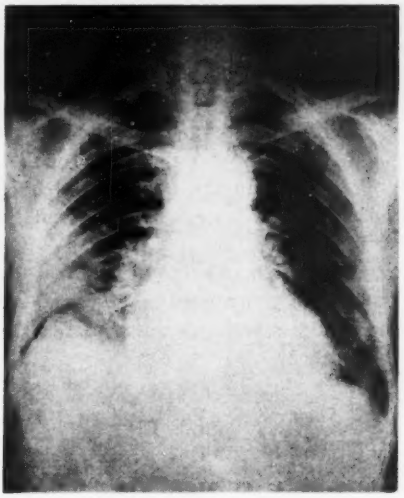

Fig. 17.—An enlarged, generally dilated type of heart. Autopsy findings were of a rheumatic type of pneumonitis.

effect due to the collagen disease, which had produced multiple focal areas of myocardial fibrinoid degeneration. Arteriolar disease was not a characteristic in this case.

In most of the cases in this group, in which the heart was thought to be involved, it was probably affected by the disease process primarily. The heart configuration on roentgen study was rather globular, owing to the generalized enlargement.

In cases in which renal involvement is present, this involvement may lead to secondary cardiac enlargement.

Liver and Spleen, or Both.—In 24 examinations of the abdomen, 13 cases, or 54%, showed the liver or spleen to be enlarged. Liver enlargement may be primarily a result of right heart failure with congestion. It is more difficult to explain the splenic enlargement; however, congestion may be the cause. In at least two cases the spleen was grossly enlarged and the liver shadow was of a normal size. It is possible that there is primary collagen disease of the spleen in scleroderma.

Miscellaneous.—Serositis was not noted as a heading, since it is difficult to evaluate; however, many cases showed pleural change, and both our necropsy cases showed pericardial involvement.

The kidneys may show involvement, and in our necropsy material striking changes were seen in the vasculature and connective tissue of the kidneys. Arteriosclerosis, arteriolar sclerosis, and arteriolar necrosis were present to a prominent degree. Glomerular loop necrosis was present. Beneath the pelvic mucosa there was present in marked degree the same proliferative alteration in the connective tissue as is characteristic of the skin. The renal involvement naturally will result in decreased function on the intravenous pyelogram.

In six cases in which maxillary sinus examinations were done, three showed roentgen evidence of marked sinusitis.

SUMMARY

A review of 63 cases of scleroderma with emphasis on the roentgen manifestations of this disease is presented.

In 57 cases in which roentgen examinations were made, 45 showed gross morphological evidence of the disease on the roentgenograms. Correlation of the roentgen appearance with the underlying pathological process is attempted, based on the collagen disturbance associated with the various vascular changes present in this disease process.

Attention is called to the fact that there was a high incidence of positive roentgen findings in generalized scleroderma. The incidence might be higher if more complete studies were obtained, particularly in generalized scleroderma with visceral involvement.

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DANGEROUS CARDIAC EFFECTS OF TETRAETHYLTHIURAM DISULFIDE (ANTABUSE) THERAPY IN ALCOHOLISM

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IN A SERIES of patients treated by us it became evident that alcohol testing [1] in patients being treated with tetraethylthiuram disulfide (Antabuse) could produce a train of severe circulatory reactions. Such experience has been noted and fatalities reported by Glud [2] and Jones [3] in patients with no demonstrable physical or laboratory abnormalities. It was felt wise, therefore, to make serial electrocardiograms of tetraethylthiuram disulfiide-treated patients while alcohol testing was being performed.

The persons used in this study were all private patients hospitalized expressly for the treatment of alcoholism. There were generally no physical complaints, although many of the patients showed evidences of vitamin deficiency and several had been treated in the past for liver disease. Without exception, all patients signified their willingness to take tetraethylthiuram disulfide. Most had been treated previously for alcoholism by other methods, with varying degrees of success. After admission and return to sobriety, a thorough medical investigation was made of each patient. Electrocardiograms, blood sugar and blood urea nitrogen determinations, complete blood cell count, liver-function tests, serologic tests for syphilis, and urinalysis were performed in each case. Tetraethylthiuram disulfide therapy was then begun. The initial dosage was 1 gm., given daily for two days, followed by 0.5 gm. daily thereafter. Where indicated by individual response to alcohol testing, the maintenance dose was raised or lowered. One-half (0.5) gram, however, was the average dose given over long periods. The first test, using 40 cc. of 100 proof whiskey, was carried out on the sixth day of therapy (the resultant amount of alcohol was, therefore, approximately 20 cc.). The second test was given on the 16th day, 20 cc. of 100 proof whiskey being employed. Subsequent tests were given as the progress of the patient warranted, using 20 cc. whiskey. During the course of each test, blood pressure, pulse rate, and respiration rate were taken every five minutes. Notes were made of the patients' reactions throughout. Electrocardiograms were taken directly prior to tests and at the height of the reaction to alcohol, but the electrodes were left in place during the entire test and tracings were taken oftener if indicated. Twenty patients, of whom 15 were men and 5 were women, were followed for more than a year in the preparation of this paper. These patients were in the fourth and fifth decades of life. No gross abnormalities were detected on physical examination or in the laboratory.

In the electrocardiograms taken at the height of the test reactions, latent coronary insufficiency or myocardial anoxia, as manifested by a total depression or deviation

of the ST segments more than 3 mm. in all four leads compared to the control, was found in four male patients (Charts 1 and 2). An additional three patients, including two women, showed inversion of T waves, especially in Leads II and III, occasionally in cR_4. Clinically, the alcohol-tetraethylthiuram disulfide reaction is

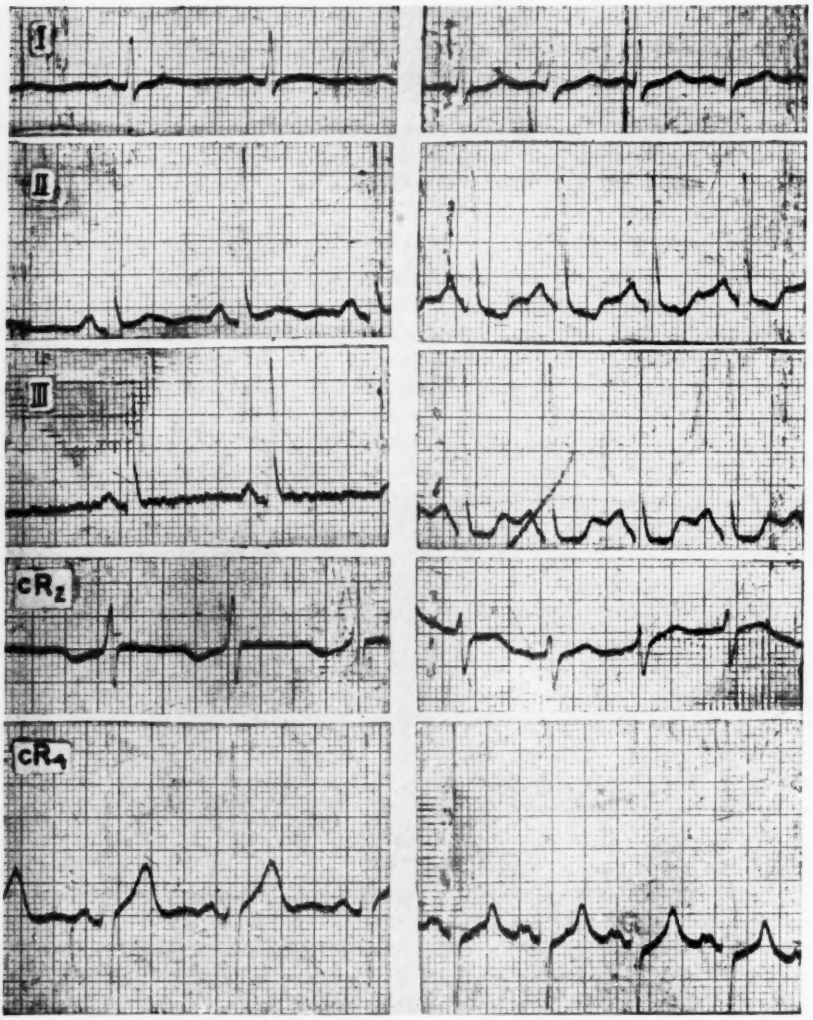

Chart 1.—Electrocardiograms of Patient J. M., on tetraethylthiuram disulfide therapy, before (left) and after (right) alcohol.

characterized by a facial flush and tachycardia, with a slight elevation in blood pressure and widening of pulse pressure. The height of the reaction occurs within 20 to 30 minutes and is dissipated within three quarters of an hour. Many patients are somnolent afterward. In five of the seven cases that exhibited electrocardio-

graphic evidence of myocardial anoxia or coronary insufficiency, there was a fall in blood pressure and a shock-like picture. In four there was a considerable degree of nausea and vomiting, and a sense of constriction at the lower end of the sternum was noted. One male patient, who previously had made an excellent recovery from a severe bout of hepatitis, had a control electrocardiogram showing a marked ST-segment elevation in Lead cR_2 but no Q wave and an upright wave. After a test dose of whiskey there was no exaggeration in cR_2, but the ST-segment elevation was also seen in cR_4. No ventricular aneurysm or pericarditis could be demon-

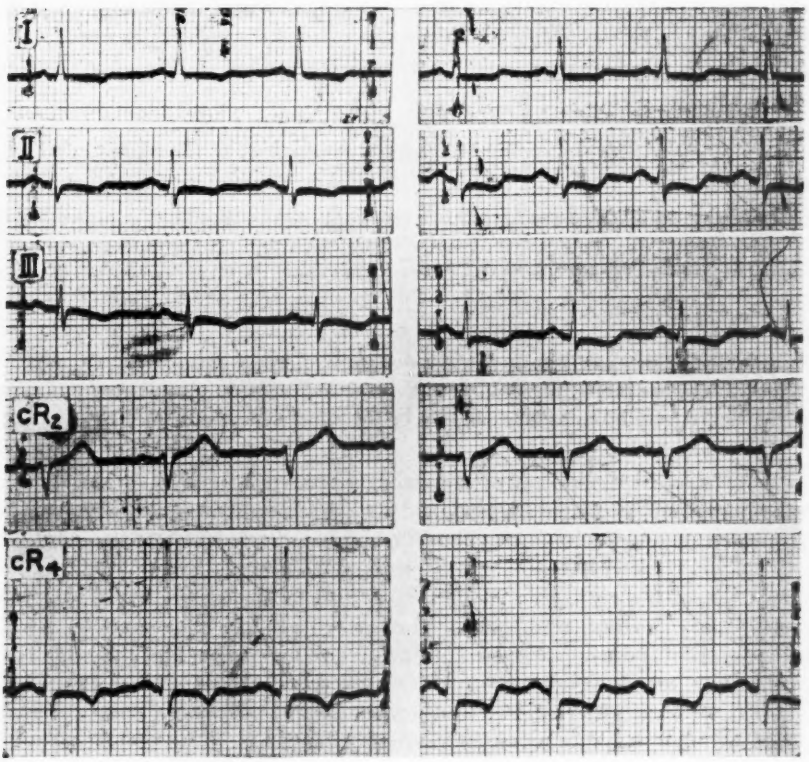

Chart 2.—Electrocardiograms of Patient R. F., on tetraethylthiuram disulfide therapy, before (left) and after (right) alcohol.

strated. Perhaps this was due to subendocardial infarction of the posterior wall. Histories of angina could not be elicited, and these patients did not have true pain but only a constricted feeling at the inferior end of the sternum.

The mechanism of the alcohol-tetraethylthiuram disulfide reaction has not been fully elucidated. It has been shown that tetraethylthiuram disulfide inhibits 85% of cellular respiration [4] as measured by the oxygen uptake of rat liver homogenates (Warburg technique). Tetraethylthiuram disulfide acts as a competitive hydrogen acceptor, since reaction time was lengthened three times over the controls. Ascorbic acid also, which is a hydrogen donor, can naturalize this inhibition. The elimination

rate of alcohol and acetaldehyde is of the same magnitude in the tetraethylthiuram disulfide-treated patient as in the control; consequently, if there is an increased level of acetaldehyde following the ingestion of alcohol it must mean that an alternate pathway of oxidation has been blocked. As tetraethylthiuram disulfide is broken down the cyanide groups act as an enzyme inhibitor,[5] for only 20% of tetraethylthiuram disulfide is excreted as such. This alone can account for the hypersensitivity to alcohol. Contraindications to the use of tetraethylthiuram disulfide would include diabetes mellitus; hepatic, renal, and severe cardiovascular disease, and epilepsy.

It is postulated that coronary insufficiency can be produced in this way, although this has not been fully established in this study. It is quite evident, however, that the physician should be sensitive to the potentially dangerous cardiac effects of the alcohol-tetraethylthiuram disulfide reaction. This reaction, of course, does not occur only in the tested patient but also occurs, unfortunately, in the patient who elects to perform his own experiment outside the confines of the physician's office or hospital.

Following an editorial comment [6] by one of us, papers * appeared which pointed out the frequency of electrocardiographic changes in the alcohol-tetraethylthiuram disulfide reaction. Ninety per cent of 40 patients were found to show one or more changes. T-wave changes appeared in 80%, and there were S-T segment changes in 60%. Surprisingly, arrhythmia other than tachycardia was rarely seen. About 20% showed a marked drop in blood pressure and major changes in the electrocardiogram. The opinion was expressed that the S-T segment changes corresponded to ventricular strain patterns, especially of the right ventricle, rather than to coronary insufficiency.

A variation in priming and maintenance dosage seen in use by various authors makes it difficult to compare results, and so standardization should be attempted. Recently, it has been shown that tetraethylthiuram disulfide potentiates cortisone activity, and if blood levels or ratio to desoxycorticosterone acetate are important stimuli to corticotropin release it would follow that the patient on tetraethylthiuram disulfiide may be a poor risk from an anesthesia standpoint. An alteration of internal metabolism and not deficiency of oxygen per se may account for the heightened conductivity on the electrocardiogram and the sluggish myocardial recovery, for ascorbic acid is a better antidote than oxygen therapy. Shock measures including use of arterenol should be promptly instituted as well.

In the cases herein presented the S-T segment change was that of coronary insufficiency. Since the pretreatment electrocardiograms were essentially negative, nothing can be said about masking left ventricular preponderance, and no right ventricular strain was demonstrated. The Q-T interval was lengthened without electrolyte change in one case.

CONCLUSIONS

Each patient prior to the institution of tetraethylthiuram disulfide (Antabuse) therapy should be exhaustively studied from a cardiac standpoint.

Thirty-five per cent of the patients in the present series showed evidence of dangerous cardiac embarrassment in alcohol-tetraethylthiuram disulfide testing,

* References 7 and 8.

despite negative cardiac history and absence of abnormal clinical findings. Special consideration, therefore, should be given to this group of patients as regards continuation of tetraethylthiuram disulfide therapy.

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PERIARTERITIS (POLYARTERITIS) NODOSA PRODUCING INTUSSUSCEPTION

Report of Two Cases

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ABDOMINAL viscera are so frequently involved in periarteritis nodosa that a gastrointestinal type has been considered one of the main clinical forms of this disease.* The symptoms considered [8] to be of gastrointestinal origin include abdominal pain, loss of weight, anorexia, nausea, vomiting, abdominal distention, hemorrhage, jaundice, and diarrhea. In general, these complaints can be ascribed to the vascular lesions, which produce either hemorrhage or infarction, although abdominal pain may occur in periarteritis nodosa without grossly demonstrable lesions in the gastrointestinal tract. Many authors † emphasize the fact that the abdominal symptoms may be sufficiently severe to suggest the need for surgical intervention, with the implication that this need is usually not corroborated by the findings at laparotomy.[10] Nevertheless, perforation of the gastrointestinal tract due to ulceration secondary to periarteritis nodosa has been described.[4] In a review of the literature, no reference has been found to the occurrence of intussusception as a result of this disease. It is, therefore, of interest to report two patients in whom lesions of visceral angiitis involving the cecum led to cecal intussusception. In one, a diagnosis of periarteritis nodosa was clearly established. The clinical and histologic features of the second patient were also those of "visceral angiitis," although not clearly of periarteritis nodosa.

REPORT OF CASES

CASE 1.—E. C., a 33-year-old white man, was admitted to the Veterans Administration Hospital, Omaha, on April 19, 1951, complaining of joint pains for two months. Asthenia, weakness, and joint aching, which developed in 1943, when he was a prisoner of war of the Germans, continued until February, 1951. At that time he developed a migratory polyarthritis, beginning with the knees. One month before admission lesions which corresponded to small

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Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

* References 1-8.

† References 2, 4, and 6-9.

discrete papules, bullae, and ulcers appeared on the extremities. Weakness and fatigability became progressively severer, vague epigastric distress occurred irregularly, and by the time of admission the patient had lost 10 lb. (4.5 kg.).

On entry he was chronically ill and pale and showed evidence of marked wasting (Fig. 1*A*). The lungs were clear; the heart was not abnormal, and the blood pressure was 116/76. Slight generalized lower abdomen tenderness was present. The joints of the extremities were stiff and painful on motion but were not warm or swollen. There were a number of rounded white atrophic scars and ulcerations on the extremities and the face (Fig. 1).

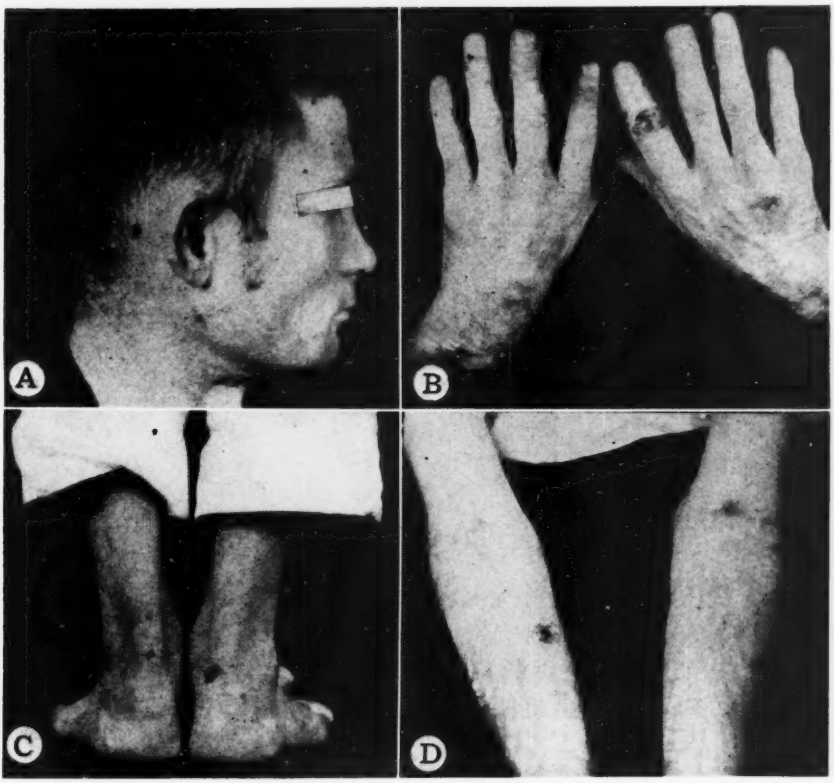

Fig. 1 (Case 1).—*A*, appearance of periarteritis nodosa (chlorotic marasmus) and a lesion of the skin; *B*, *C*, and *D*, other skin lesions.

Laboratory studies revealed a mild anemia, slight increase in circulating eosinophiles, and an abnormal urinary sediment.

During the next few months the patient continued to appear chronically ill, failed to gain weight, and had persistent arthralgia and complained frequently of epigastric and periumbilical cramping pains and nausea. The temperature rose to 99 F. occasionally. On Dec. 19, 1951, he developed unusually severe pain in the right lower quadrant, followed by nausea and vomiting. Examination revealed a tender mobile 6 by 4 cm. mass, located 5 cm. to the right of the umbilicus. During the succeeding four hours the mass doubled in size. Although a diagnosis of massive retroperitoneal hemorrhage was entertained, the mobility and discreteness of the mass suggested that it might be intraperitoneal.

Laparotomy revealed a readily reducible intussusception of the cecum into the ascending colon, caused by a granulomatous lesion in the tip of the cecum. The indurated edematous base of this plaque formed a tumor-like nodule, which led the intussusception. Althought it was readily reducible, the danger of its reformation and of subsequent perforation warranted hemicolectomy.

The resected specimen was composed of a loop of bowel consisting of an 8 cm. segement of terminal ileum, the cecum and appendix, and the ascending and a portion of the transverse colon (Fig. 2*A*). The cecum and terminal ileum were edematous and moderately reddened. The distal one-half of the appendix and the mesenteric fat were dark red. On the serosal surface of the cecum was a thickened granular puckered area measuring 2.5 by 5.8 cm. Within the lumen of the cecum a 7 by 5 cm. dark red edematous mass protruded.

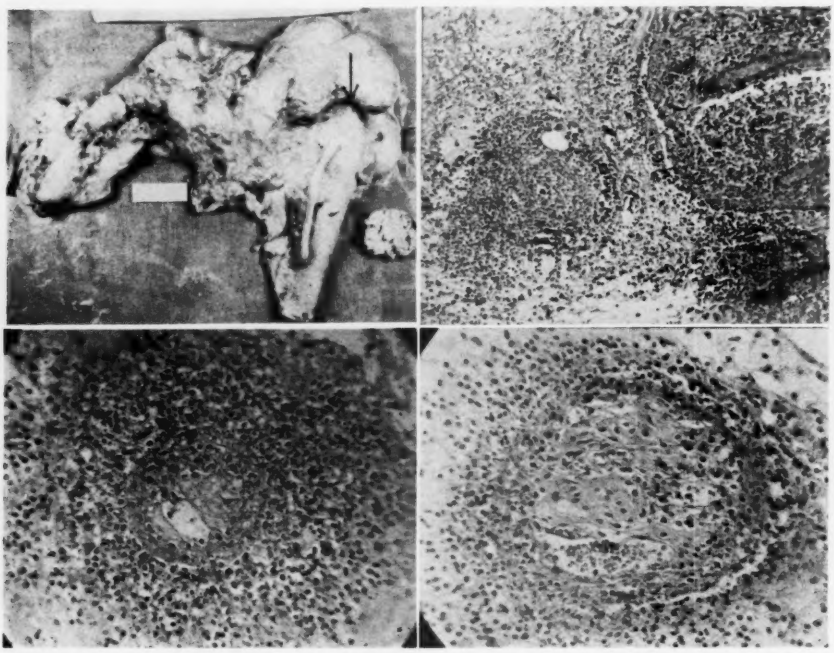

Fig. 2 (Case 1).—*A* (upper left), surgical specimen, showing granuloma of cecum; *B* (upper right), photomicrograph of section from grauloma, showing intense inflammation of the mucosa and submucosa centering about vascular spaces; × 72; *C* (lower left), acute inflammation in a small arteriole; × 153; *D* (lower right), older thrombosed vessel with recanalized and residual inflammation; × 153.

Sections taken from this mass (Fig. 2*B*, *C*, and *D*) showed marked edema of all layers of the wall, extravasation of red blood cells, and necrosis and ulceration of portions of the mucosa. The most prominent change was a marked inflammatory reaction of blood vessels. In many areas the small arteries and arterioles showed segmental necrosis and fibrinoid degeneration of the wall, associated with infiltration of polymorphonuclear leucocytes, eosinophiles, and lymphocytes. The internal elastic membrane could not be demonstrated in most of the vessels, and the intima was frequently destroyed. Involvement of veins was present but was more sporadic. An inflammatory exudate was observed along the serosa in some areas. Sections of the appendix showed inflammatory exudate on the serosa and minimal involvement of the vascular channels in the mesoappendix but no evidence of a primary appendicitis. Histologically, the changes in this intestine were those of periarteritis nodosa.

Recovery from the operation was uneventful. During the next five months there was no consistent change in the patient's condition despite treatment with cortisone (300 mg. initially and a maintenance dose of 100 mg. daily for one month). On May 14, 1952, he developed persistent cramping abdominal pain, which contiued for the next four days. On the fifth day the pain suddenly became severe and knife-like, occupying the entire abdomen. On examination the abdomen was flat and rigid, with generalized and rebound tenderness, maximally referred to the right lower quadrant. Examination of the blood and urine showed no significant change from the previous findings. A roentgenogram of the abdomen revealed free air beneath the right diaphragm, and at laparotomy a perforation of the intestine at the site of the previous anastomosis was found. Approximately 6 cm. of ileum and 6 cm. of adjacent colon were resected, and an ileocolic anastomosis was again established. The surgical specimen revealed acute inflammation, with perforation of the intestine and periarteritis nodosa in a "healing stage." The postoperative course was uneventful. In the 14 months that have elapsed since the operation, there has been no substantial change in the patient's condition.

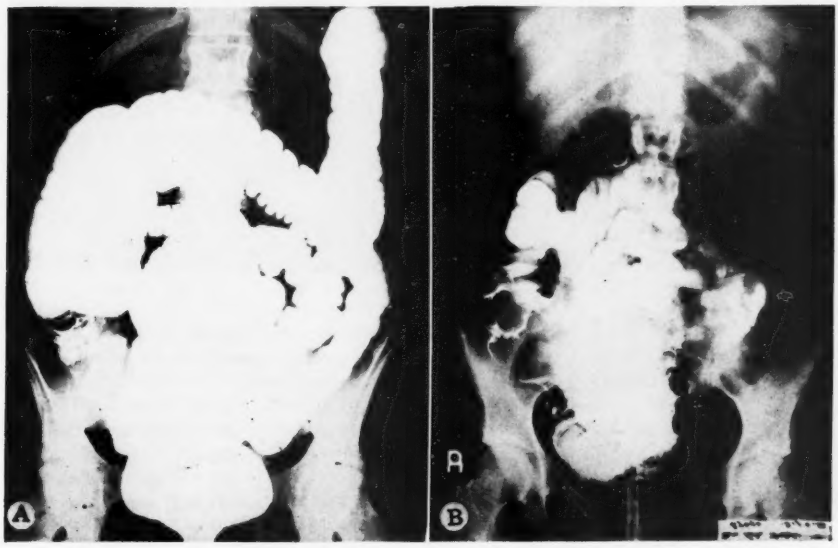

Fig. 3 (Case 2).—*A*, roentgenogram of large bowel, showing ring-like lesion of intussusception; *B*, air-contrast study, showing filling defect of cecum.

CASE 2.—Mrs. S. N. W., a 36-year-old white housewife, was admitted to Immanuel Hospital, Omaha, on March 10, 1953, complaining of severe upper abdominal cramping pain for two days. She had been well until the summer of 1949, when frequent episodes of numbness and coldness of the left second and third fingers were noticed. These symptoms were unrelated to exposure to cold or use of the hand. The subungual and perungual areas of the involved fingers were frequently tender, and at times a purulent exudate was discharged from these areas. She also noticed soreness of the palmar aspect of the left forearm and the right hypothenar muscles. She admitted smoking 20 cigarettes daily. Roentgenograms of the neck revealed no cervical ribs. Treatment at that time included limitation of smoking, administration of benzazoline (Priscoline), and avoidance of exposure to cold. Some improvement in symptoms was noted. In March, 1952, the patient's only pregnancy resulted in the delivery of a normal child. In September, 1952, she noticed aching of the calves after walking, stair-climbing, or exposure to cold. Examination at that time revealed absence of the ulnar, dorsalis pedis, and posterior tibial pulsations bilaterally. Two months before admission to the hospital she developed vague upper abdominal cramps, which were worse in the morning but associated with no change in bowel

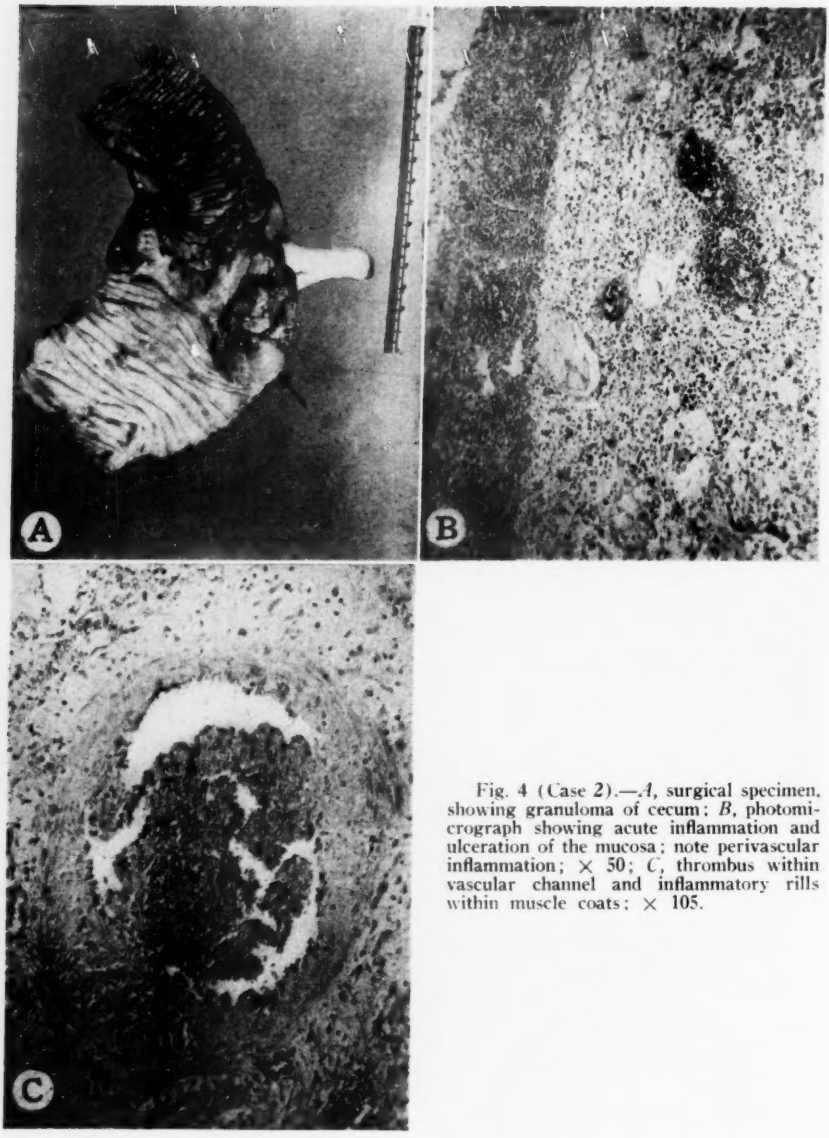

Fig. 4 (Case 2).—*A*, surgical specimen, showing granuloma of cecum; *B*, photomicrograph showing acute inflammation and ulceration of the mucosa; note perivascular inflammation; × 50; *C*, thrombus within vascular channel and inflammatory rills within muscle coats; × 105.

habit. Two days before admission severe upper abdominal cramping pain occurred, which was associated with two loose bowel movements. On the day of admission eight liquid stools containing bright red blood and clots were passed.

On admission to the hospital the patient was found to be slender but well developed and in moderate distress from abdominal pain. The temperature was 98.8 F., and the blood pressure, 116/66. There was cyanosis of the left middle finger and exfoliation of skin about the nails of the middle and second fingers. These fiingers were colder than the corresponding ones of the right hand. There was tenderness in the right lower abdominal quadrant, with a poorly defined sausage-shaped mass in this area, without rigidity of the abdominal muscles. The remainder of the physical examination revealed no abnormalities. The stool passed on the day of admission contained bright red, bloody mucus.

Laboratory studies revealed a slight leucocytosis, mild eosinophilia, and hyperglobulinemia. A roentgenogram of the abdomen revealed no evidence of intestinal obstruction, but, after a barium enema, filling defect in the base of the cecum with a ring-like formation across the cecum suggestive of intussusception was demonstrated (Fig. 3*A*). Postevacuation films and air-contrast studies revealed a persistent round filling defect in the center of the cecum (Fig. 3*B*).

Laparotomy, performed by Dr. John C. Kennedy, on the day after admission, revealed a firm regular tumor-like mass in the lateral wall of the cecum (Fig. 4*A*). This mass produced an invagination of the lateral cecal wall to a depth of approximately 2 cm. The ileocolic lymph nodes were enlarged. A right hemicolectomy and ileocolostomy were performed.

The resected specimen (Fig. 4*A*) consisted of a segment of terminal ileum, the cecum with appendix, and a small portion of ascending colon. There was a depressed firm area measuring approximately 1.5 cm. in diameter on the lateral serosal surface of the cecum. When the intestine was opened, there was found a 4.5 by 4.0 by 2.3 cm. mass which extended into the lumen of the cecum, just above the appendiceal orifice. The attached appendix was not grossly abnormal.

Microscopic studies (Fig. 2*C* and *D*) showed massive necrosis and ulceration of the mucosa of the cecal mass. The adjacent intestinal wall demonstrated marked acute inflammation, edema, and hemorrhage. The inflammatory reaction was most prominent in and about blood vessels. Some of the vascular involvement demonstrated thrombosis and diffuse inflammation of the arteries and veins as well as fibrinoid masses beneath the intima of the arteries. Eosinophiles were prominent in the cellular infiltrate. The mesenteric lymph nodes showed a nonspecific response to inflammation. The appendix was not unusual. Histologically, the changes demonstrated in this intestine were suggestive of periarteritis nodosa, but other types of visceral angiitis could not be excluded.

The postoperative course was uneventful. There has been no evidence of generalized disease in the ensuing four months.

COMMENT

The presence of intussusception was demonstrated at laparotomy in the first patient (E. C.) and by roentgenography in the second (S. N. W.). The abdominal pain and mass and the passage of blood and mucus by rectum, as well as the roentgenographic studies, supported the diagnosis of the previous existence of intussusception in the second patient, which was resolved before laparotomy. In both patients granulomatous lesions, due to vascular disease, were responsible for the intussusceptions.

Intussusception is much less frequent in adults than in children, but it is more frequently associated with demonstrable lesions of the bowel in the former than in the latter.‡ Tumors, diverticula, hypertrophied lymphoid tissue, and ulcerations are the most frequently associated lesions,§ but granulomatous and inflammatory lesions associated with tuberculosis,[16] amebiasis,[17] and typhoid fever [18] have also been reported to produce intussusception. No report of a vascular lesion of the bowel causing this condition has been found.

‡ References 11-15.

§ References 10-15.

The histologic features of the cecal granuloma in the first case were compatible with a diagnosis of periarteritis nodosa. The arthralgia, anemia, fever, skin lesions, and microscopic findings in the urine all suggested this diagnosis before histologic confirmation was afforded by examination of the surgical specimen. In the second patient, S. N. W., the clinical diagnosis of intussusception was entertained on her admission to the hospital but the possibility of a "collagen" disease had not been considered, despite the Raynaud-like phenomena and the elevated level of serum globulin. The histologic features of the specimen from this patient were those of a visceral angiitis, but neither the clinical data nor the pathological findings in the surgical specimen from the second patient provided unequivocal evidence for the diagnosis of periarteritis nodosa. Whether the picture presented by this patient was that of a generalized visceral angiitis resulting in the granulomatous lesion or whether this was a variant of the localized appendiceal arteritis of Plaut,[19] it is reasonable to assume that the intussusception was related to the granuloma. In both patients, therefore, intussusception was produced by a granuloma of vascular origin. The abdominal complications of periarteritis nodosa usually result from occlusion or rupture of diseased arteries. It has been emphasized that these patients are frequently explored, because their condition may simulate an acute surgical emergency,‖ although the findings at laparotomy do not usually support this clinical impression. Hence, caution in recommending surgery for episodes of abdominal pain in patients with this disease would seem wise as a general policy.

The two patients presented here, however, illustrate that abdominal complications of visceral angiitis may at times produce true surgical emergencies. Perforation of a hollow viscus due to involvement by periarteritis nodosa has also been described,[4] and this would constitute another example of a surgical emergency in this disease. Even segmental infarctions may lend themselves to surgical removal, permitting survival of a patient who might otherwise die.

The importance of the characteristic abnormalities of the urinary sediment in the diagnosis of visceral angiitis was first emphasized by Krupp.[20] Several subsequent reports ¶ have corroborated his observations that the finding of a "telescoped" sediment in the urine is highly suggestive or, indeed, diagnostic of this group of diseases. The first case illustrated this feature. The clinical diagnosis of periarteritis nodosa was made in this patient because his urine contained red bood cells, granular cells, oval fat bodies, and fatty casts, although at no time were more than a few "broad casts" demonstrated. The presence of abnormalities of the urinary sediment suggestive of both acute and chronic nephritis in a patient whose clinical features are otherwise compatible with a collagen disease may be considered diagnostic.[20] No abnormalities of the urinary sediment were demonstrated in the second patient, although the urine was carefully scrutinized on a number of occasions.

SUMMARY AND CONCLUSIONS

Two patients with intussusception due to visceral angiitis of the cecum are described. In one patient the diagnosis of periarteritis nodosa was established by

‖ References 2, 4, 6, 8, and 9.

¶ References 21 and 22.

the clinical, laboratory, and histopathologic studies. In the other patient, the clinical and histological features, while not clearly those of periarteritis nodosa, were in the category of a "visceral angiitis."

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Progress in Internal Medicine

INFECTIOUS DISEASES

Nineteenth Annual Review of Significant Publications

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IN THE past year contributions to knowledge in the field of infectious disease, as usual, included a wide variety of subjects. No spectacular advances were reported. Antibiotic therapy continues to hold the most interest. Enormous amounts of antibiotic agents are used, but increasing information about illogical and indiscriminate therapy and of harmful side-effects eventually will bring about their more rational application. Minor infections of the respiratory tract, viral hepatitis, Coxsackie disease, tuberculosis, and streptococcosis were subjects of intensive investigation. Opinion has formed regarding the value of gamma globulin to prevent poliomyelitis, and interest now rests on the results of prophylaxis with a vaccine. Since its control with penicillin, lobar pneumonia has scarcely been mentioned, and a journal devoted to syphilology is about to be abandoned for want of interest.

ANTIBIOTICS

The list of infectious diseases known to be influenced favorably by antibiotic therapy is fairly stable and needs but little comment. These diseases are seldom encountered in average general practice and few patients attended by practicing physicians need antibiotic therapy. Discussions of modern views on the subject were written by Spink [1] and by Finland.[2]

Antibiotics continue to be used indiscriminately at a rate which led Jawetz to estimate that only 5% of them is used properly.[3] I had previously suggested 10%. In one hospital in New York City, 75% of patients had had antibiotic therapy before bacteriologic study was made. Of these, 40% received penicillin; 30% received penicillin and another antibiotic, and 30% were given one or more antibiotics other than penicillin.[4] Unnecessary therapy adds to the high cost of medical care. Critical appraisal of indications for the use of antibiotics and restraint of therapeutic exuberance serve to reduce the expense. For example, here in the 216-bed American University Hospital, the prescription of penicillin was reduced from about 8,000 vials in 1952 to about 5,000 in 1953; that of streptomycin, from 6,000 to 3,000 vials; that of chlortetracycline from 158 to 21 vials, and that of chloramphenicol, from 264 to 33 vials. At cost price to patients, the decline in use represents a saving of over $4,000.

According to last report, 30 tons of pencillin were manufactured monthly in the United States. The rate has increased since then in both domestic and foreign production. In consideration of this prodigious supply, its consequent waste in unnecessary therapy, and the actual and potential harm done thereby, it seems

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fitting to dwell on this aspect of the matter. There are four major harmful side-effects of antibiotic therapy—hypersensitization, toxicity, induction of bacterial resistance, and replacement of flora.

Hypersensitization.—All the manifestations of serum sickness may follow the injection of penicillin or streptomycin or the use of sulfonamide therapy. Cutaneous and mucosal lesions; arthralgia; gastrointestinal, hepatic, and urinary tract disturbances; nervous disorders; blood dyscrasias, and other allergic manifestations have been observed. Their occurrence is unpredictable; patients reacting unfavorably to antibiotics on one occasion may not do so on another. Hypersensitive reactions may, at times, be controlled with adrenocorticotropic hormone therapy.[5] Editorial comment on the subject is worth reading.[6]

Severe and fatal reactions to penicillin are occurring with increasing frequency as more and more persons are sensitized by legitimate or indiscriminate treatment with it.[7] A case was observed in which penicillin procaine given for a minor infection caused severe urticaria and illness for five weeks. After a recurrence, cortisone was administered, which in turn seemed to reactivate varicella.[8] Curphey observed two fatalities after the intramuscular injection of penicillin in asthmatic patients.[9] Another death followed injection of penicillin procaine.[10] Fourteen severe anaphylactoid reactions and 3 deaths followed the administration of penethamate hydriodide, a preparation of pencillin which is said to have an affinity for lung tissue.[11]

Mayer and his associates had no difficulty in detecting six patients in a short time who had had serious anaphylactic-like shock after injection with penicillin.[12] One died. All six had previously received penicillin. In one, an almost fatal reaction followed an intradermal skin-test. They infer that many more instances occur than is realized. All patients should be asked before therapy if a previous reaction to penicillin has occurred. If so, a skin test with a high dilution of penicillin should be made. No reliance should be placed on attempts at desensitization.

Local or topical therapy particularly is apt to induce hypersensitivity. In Kutscher's study, from 38 to 76% of patients who had received troches containing either penicillin, chlortetracycline, or oxytetracycline had allergic reactions.* Official recognition of penicillin dispensed in troches was withdrawn in 1949 by the Council on Pharmacy and Chemistry of the American Medical Association.

Toxicity.—Hepatorenal fatty degeneration was observed in a fatal case in which 4.8 gm. of chlortetracycline had been given intravenously over four days.[15] No new facts accrued regarding the toxicity of chloramphenicol or streptomycin.

Induction of Bacterial Resistance.—From 60 to 75% of strains of staphylococci recently isolated from patients are resistant to penicillin; about 25% resist chlortetracycline or oxytetracycline, and 17% resist chloramphenicol.† Bacteria resistant to chlortetracycline may be resistant to oxytetracycline (Terramycin) and to chloramphenicol (Chloromycetin). Cross resistance also occurs between streptomycin and neomycin and between carbomycin (Magnamycin) and erythromycin (Ilotycin).[18]

The problem of cross resistance is complicated. Staphylococci and enterococci rendered resistant to erythromycin or streptomycin were found to be resistant to

* References 13 and 14.

† References 16 and 17.

the homologous antibiotic but not to the other one. Cross resistance to neomycin appeared in staphylococci resistant to streptomycin, but such cross resistance to neomycin did not occur in strains resistant to erythromycin. Apparently, development of resistance to penicillin, streptomycin, or erythromycin in vitro may be delayed and depressed by combining erythromycin with either penicillin or streptomycin.[19] How complicated the problem is is indicated in this quotation:

> For suppression or delay in the development of resistance to one of a pair of antibiotics to which bacteria are simultaneously exposed, both of the antibiotics must exert an inhibitory activity; if the strain is resistant to one of the pair of antibiotics, its presence in a high but ineffective concentration may not influence the development of resistance to the second agent.[20]

Replacement of Flora.—The administration of chlortetracycline or oxytetracycline suppresses the growth of bacteria sensitive to these agents. In the intestinal tract, staphylococci, which may be present in small numbers and are resistant to these antibiotics, may then multiply rapidly. Dearing and Heilman report on 44 cases in which mild to severe enteritis was caused in this manner.[21] Several patients died. Three fatal and two nonfatal cases were reported by Fairlie and Kendall.[22] Staphylococcic enteritis in mild form disappears when antibiotic therapy is stopped and the normal flora returns. It may respond to treatment with erythromycin. Unfortunately, resistance to erythromycin also may develop.

In a large hospital service, one third of the bacteria cultivated from patients were unusual ones, chiefly colon, proteus, and pyocyaneus bacilli. These were present in locations in which they were not often found in the preantibiotic era.[4] A patient who received adrenocorticotrophic hormone and chlortetracycline for periarteritis developed monilial peritonitis. In another case, fatal agranulocytosis with disseminated aspergillosis and moniliasis followed therapy with chloramphenicol.[24]

A German observer believes that second attacks of scarlet fever may occur after therapy of the first attack with penicillin. He believes that they occur because therapy prevents the development of adequate immunity.[25] According to Jawetz, cortisone hampers the therapeutic effect of antibiotics in experimental studies in mice.[26]

General Therapy.—On the basis of weight, the following agents are most effective against staphylococcic infection: erythromycin, chlortetracycline, oxytetracycline, bacitracin, streptomycin, chloramphenicol, neomycin, polymixin B, and penicillin. Only about 20% of strains were sensitive to penicillin, and for these penicillin is the drug of choice.[16]

In cultures of staphylococci grown in the presence of penicillin, minute "G" variants have been detected. These are resistant to penicillin and are avirulent, but when cultivated without penicillin they revert to the original large colony virulent parent form. The minute colonies unless sought can easily be overlooked. G forms harbored in the body may revert to the original form if antibiotic therapy is stopped.[27]

Exception may be taken to a recommendation to treat mild sore throat or rhinitis with daily doses of 400,000 units of penicillin.[17] The majority of such infections are not caused by bacteria and need no specific therapy. Moreover, the dose recommended is even greater than is needed to cure pneumococcic lobar pneumonia of average severity.

According to Magill and Killough, oxytetracycline together with streptomycin administered for three weeks gave good therapeutic results in 22 patients with brucellosis.[28] Relapse occurred in 14%. Oxytetracycline was used successfully in the treatment of severe cases of actinomycosis. Doses of 750 to 2,000 mg. daily for two to six weeks were used. Relapse in one patient was controlled by resumption of therapy. Incision and drainage are carried out as needed. In almost all patients in Korea with bacillary dysentery, sulfonamide therapy, contrary to earlier reports, had no beneficial effect, because the Shigella organisms were resistant to the drugs. Oxytetracycline, chlortetracycline, or chloramphenicol in doses of 4 gm. in three divided doses in 24 hours were effective in therapy.[29] Another author recommends sulfonamide compounds as highly effective in treating bacillary dysentery.[30]

The results of the treatment of 294 children with whooping cough were not spectacular. The best that could be said by an English committee was that early recognition and therapy with chlortetracycline or chloramphenicol may help to reduce the severity of the infection, but little is gained from treatment in cases in which even mild symptoms have been present for over a week.[31]

According to a bulletin published in 1951, antibiotics have yet to be proved of value in the treatment of cholecystitis with or without empyema.[32] Subsequent studies have not advanced their position much. Acute obstructive calculus cholecystitis was not influenced significantly by antibiotics. They may be successful in cases of noncalculus acute cholecystitis. Benefit was observed when the systemic symptoms were severe, but there was little effect on the local process. Empyema of the gall bladder occurred regardless of treatment. Antibiotics are said to fail if obstruction is present.[33] It is doubtful if the amount of antibiotics in the lumen of the gall bladder is of more importance than that which reaches the infection in the walls by way of the blood stream.

In a series of papers abstracted in the *Tropical Disease Bulletin* of Sept. 20, 1953, are reports of no beneficial effect of either chloramphenicol or oxytetracycline in the treatment of cholera.

Combined Antibiotic Therapy.—The problem of multiple antibiotic therapy is discussed by Dowling and his associates.[34] In brief, a single antibiotic is advised in most instances of infection caused by a single kind of bacterium. One broad-spectrum antibiotic may be used in mixed infections caused by rupture of a viscus, but occasionally even here penicillin may be sufficient to control the most pathogenic germ. The following combinations are said to be useful at present: streptomycin plus chlortetracycline, chloramphenicol, or oxytetracycline for brucellosis or serious staphylococcic infection; penicillin plus streptomycin for enterococcic endocarditis, and streptomycin plus *p*-aminosalicylic acid or isoniazid for tuberculosis. Combined therapy may be needed in other infections if in vitro tests of sensitivity of the causative organism so indicates. The subject is discussed also by Garrod.[35]

No evidence of antibiotic antagonism was observed in 25 patients with pneumococcic pneumonia treated with a combination of penicillin and chlortetracycline. However, after initial improvement in five, Staphylococcus aureus in pure culture was recovered from the sputum and cavitation developed in two. One died from staphylococcic pneumonia.[36]

Neomycin and oxytetracycline given orally in combination are effective in eliminating many aerobic and anaerobic bacteria from the intestinal tract. Their use one day preoperatively is recommended to prepare the intestine for surgical operation.[37]

New Antibiotics.—Fierce commercial competition is largely responsible for the variety of newly discovered antibiotics, according to editorial remark.[38] Nystatin, hygromycin, streptogramin, cardicidin, streptocardin, ruticin, and puromycin were discussed at a symposium on antibiotics.[39] Evidently a new branch of language is in formation. Confusion in nomenclature is bound to arise, since Chloromycetin is officially chloramphenicol; Aureomycin is called chlortetracycline, and Terramycin is oxytetracycline. To add to the problem, tetracycline, a dehalogenated chlortetracycline, is called Achromycin. One wishes that simpler names had been coined.

In Bunn's experience, the results of the treatment of pneumococcic pneumonia with carbomycin and erythromycin were so unsatisfactory that further study was discontinued.[40] Finland also does not recommend carbomycin as a useful agent.[41]

Luckily, at present at least, erythromycin is available to control infection with staphylococci which are resistant to other antibiotics.[42] Erythromycin successfully controlled staphylococcic infection in about half of 17 cases of involvement of bony and soft tissues. It seemed to save the life of six of eight patients with septicemia. In the other two, the cocci became resistant. This is ominous. If erythromycin is used as routinely or as indiscriminately as other antibiotics are it may not be long before a high percentage of strains of staphylococci will become resistant to it also. This will demand the use of another new antibiotic. Will one be discovered?

Report elsewhere confirms the prediction just cited. Lepper reported the presence of erythromycin-resistant staphylococci in healthy carriers. The use of the antibiotic should be restricted to the treatment of infection with penicillin-resistant staphylococci.[39]

Erythromycin and carbomycin are broad-spectrum antibiotics and may be classified with chlortetracycline, chloramphenicol, and oxytetracycline as regards their effects in combination with other antibiotics. When combined with penicillin they may hinder or enhance its bactericidal effect.[43]

Search is under way to discover antibiotics active against fungi and viruses. Some success is reported.[44] Candicidin is said to be fungistatic and fungicidal. It protected mice infected with Candida albicans, Blastomyces dermatitidis, and Sporotrichum schenckii but was not effective against Cryptococcus (Torula) and Histoplasma.[45] Neotropin, an antibiotic derived from a variety of Streptomyces, is effective against the virus of vaccinia but not against other viruses. A penicillium filtrate called 8450 is somewhat effective against MM, Semliki Forest virus, and a poliomyelitis virus.[46]

In a series of papers in the May, 1953, issue of the *Journal of Experimental Medicine*, Shope describes an antibiotic derived from Penicillium funiculosum named helenine after Helen, his wife. When given to mice infected with encephalomyelitis virus or Semliki Forest virus it prolongs life and at times permits survival. Another substance, active against swine influenza virus infection in mice, was lost. The mechanism of action of helenine is unknown. It may have no practical value, but it apparently is one of the first antiviral antibiotics discovered. Helenine may be related to the antiviral substance described by Powell and his co-workers.[46]

DISEASES OF VIRAL OR PROBABLE VIRAL ORIGIN

Infections of the Respiratory Tract.—Three statistical studies emphasize the importance of minor respiratory tract infections as regards the demand for medical services in general practice. A group of physicians analyzed 1,000 consecutive visits to homes. Minor infections of the respiratory tract and gastrointestinal tract accounted for 378 visits, far outnumbering other reasons for which the physicians were called. Influenza, tonsillitis, colds, and gastroenteritis headed the list. Only 70 visits were for pneumonia. The great majority of infections were those in which antibiotic therapy has no beneficial effect.[47]

In a tabulation of family groups in Cleveland, minor respiratory tract infections accounted for two-thirds of illnesses. Only 2.5% of infections were caused by Group A streptococci or pneumococci. Persons had on an average of six colds per year. The incidence was greatest in early life and declined in proportion to age.[48] It would seem that the best way to escape colds is to grow older. In England, minor infections of the respiratory tract account for 24% of calls for medical aid.[49]

Atlas has four filtrable cold-producing agents, three of which were cultivated in embryonated eggs. Inoculation of volunteers with each virus caused symptoms of minor respiratory tract infection. Two agents evoked no immunity to reinfection several weeks later; resistance to reinoculation with the other two persisted for one to eight months. Pretreatment and continual therapy of volunteers with antihistaminics and antibiotics were without prophylactic or therapeutic effect.[50]

After many failures in a seven-year investigation Andrewes and his co-workers now report the cultivation of the virus of the common cold through 10 serial cultures in embryonic human lung tissue. Evidence of its growth and multiplication was gained by infecting volunteers. The clinical response was similar in volunteers infected by cultivated virus or by nasal washings from victims. Symptoms varied in severity in both methods.[51]

A report has been made by the Virus Reference Laboratory, in London, to which samples of serum are sent for the diagnosis of viral infections. In a two-year period, samples from 1,660 patients were received, but only one-third of them were collected properly, that is, one sample during the acute phase and another in the convalescent phase. Clinical diagnoses included influenza, colds, bronchitis, and pneumonia. About 30% of the samples tested had antibodies against one or several viruses. Among 551 samples, 16% gave serologic evidence of influenza, 8% agglutinated Streptococcus MG, 5% were positive for Q fever, and 1% were positive for psittacosis.[52]

Influenza.—Francis gives reasons why he believes that the pandemic of influenza of 1918-1919 was caused by a virus related to the current influenza A virus.[53] It is still unknown, however, why the virus of the pandemic was so virulent, why it caused death occasionally in a toxic shock-like state even without secondary bacterial pneumonia, and why secondary bacterial pneumonia occurred so often.

Influenza A appeared in Ireland in 1951. In studies made on pregnant women at the time, 116 were sick during the first trimester. Of the infants, born later, three had congenital defects and three were stillborn. This is said to be higher than the rate of defects in infants born of well women and may suggest that influenza virus may be teratogenic, though not so often as rubella.[54]

During the winter of 1952, influenza viruses C and B were isolated from patients with mild infection of the respiratory tract. Some had symptoms like those of the common cold. Virus could not be recovered nor immune reactions demonstrated in some patients who had influenza-like symptoms.[55]

According to Magill and Jotz, who studied many strains of virus isolated during 18 years, the change in antigenic constituents has progressed in an orderly manner. Complexes found in early isolated strains have been replaced by others in recent years.[56] One view holds that A viruses deviate antigenically each year, whereas B strains isolated since 1943 are closely related and seem to have fairly stable antigens.[57]

To classify the numerous subtypes of influenza A viruses, Hirst has set up six main type-specific antigenic components, but more, no doubt, will be added. Of the strains thus far studied, only one failed to have one type-specific component together with group-specific antigen which characterizes the influenza A group.[58] Apparently, differences in strains encountered from year to year may evolve through the process of variation or mutation.

A committee on influenza of the World Health Organization has published a report describing standardized methods of grouping of influenza viruses, of collection of specimens for diagnosis, of diagnostic procedures, of training laboratory workers, and of preparation of antiserums.[59]

Influenza vaccines available at present hold little promise of being able to eliminate the disease.[60] Even if specific vaccine is used, the best that can be hoped for it is to limit an epidemic by reducing the number of infections. This happened in a Swiss experiment in which vaccine containing the strain of virus which caused a current epidemic was used. The morbidity from influenza was 4.5% among those vaccinated as compared with 8.4% in the control subjects. Fever, fatigue, and arthralgia was caused by vaccination in one-third of the group. Local reactions, such as redness, nodules, and pustules, occurred in 94% of persons vaccinated by the two-stage intracutaneous method and in 48% after subcutaneous inoculation. Five months later, nodules or scars still were present in 83%.[61] One wonders if the reaction to the vaccine was not worse in many cases than having influenza itself.

Influenza virus inoculated intraperitoneally, in contrast with that inoculated intranasally, causes lesions in the alveolar walls and small blood vessels in the periphery of the lungs and in the pleura. The bronchial lining seems to be involved secondarily. The difference may explain the clinical variation in human influenza if virus reaches the lungs by different routes, in one case as a primary infection of the respiratory tract, in the other as a systemic blood-borne infection with incidental involvement of the respiratory tract.[62]

Oxytetracycline and erythromycin given to persons with influenza and other nonbacterial respiratory tract infections caused no beneficial effect. Acetylsalicylic acid (Aspirin) gave relief from symptoms. There was no evidence that the antibiotics used prophylactically served to prevent secondary bacterial infection.[63]

A great amount of information about influenza was published in a bulletin issued by the World Health Organization.[64]

Viral Pneumonias.—The British attitude toward viral pneumonia is outlined by James. Viral pneumonia comprised about 11% of cases of pneumonia seen in a London hospital in 1949-1950. He contradicts the extreme view of some English physicians who hold that what is called viral pneumonia is nothing but aspiration pneumonia. Among other differential features, viral pneumonia commences with

constitutional symptoms and is not influenced by penicillin or sulfonamides. Aspiration pneumonia begins with an upper respiratory tract infection or other cause and may respond to therapy with penicillin or postural drainage.[65] No mention is made of the large epidemic of viral pneumonia of 1941-1943 or of subsequent small ones. Cranshaw criticizes the abuse of the term viral pneumonia. Care must be taken not to confuse the disease with early pulmonary neoplasm, tuberculosis, bronchiectasis, or aspirated foreign bodies.[66] The uncertainties of diagnosis and nomenclature will persist until the cause or causes are discovered.

In a controlled study, groups of patients with viral pneumonia were treated, respectively, with penicillin, chlortetracycline, oxytetracycline, and a placebo. Chlortetracycline and oxytetracycline had no effect on the rapidity of disappearance of pulmonary infiltration.[67] In a similar study, of 212 patients, chlortetracycline had no influence on any aspect of the disease.[68] It was not antipyretic, as had been suggested previously.[69]

Three cases of severe varicella with specific viral pneumonia were observed in adults.[70] Two cases of a rare form of cytomegalic inclusion pneumonitis in adults due to the salivary gland virus were diagnosed during life by means of biopsy of the lung. A peculiar histopathologic response was present in both.[71] In the absence of a demonstrable cause, a newly recognized pulmonary disease, namely, interstitial fibrosis of the lungs, was suggested to be caused by a virus.‡

A form of pneumonia in swine previously thought to be caused by Pasteurella was found to be viral in origin. It could be transmitted to pigs but not to other animals or to chick embryos.[74]

Viral Hepatitis.—Controversy persists as to whether infectious hepatitis and serum hepatitis are identical diseases which differ clinically only because of different portals of entry. Some evidence suggests that they are different entities. There is a difference in the duration of the "incubation" period and lack of cross immunity; gamma globulin is said to confer protection against infectious hepatitis but not against serum hepatitis, and epidemics of the latter variety do not occur. Infectious hepatitis, in contrast with serum hepatitis, mostly affects young persons, and carriers are less common.[75]

Deschamps and Steer report on 2,351 patients with liver disease among American troops in the Far East. Viral hepatitis was diagnosed in 2,030. They describe methods of diagnosis and the indication and method for needle biopsy of the liver in 84 patients. Biopsy is valuable in diagnosis and in determining the course of the disease. No untoward effects were noted.[76]

Of 255 wounded soldiers who had received plasma, 56, or about 22%, developed hepatitis regardless of whether the plasma was irradiated or not. Of 332 who received infusions of blood, only 12, or 3.6%, developed jaundice.[77] In one series of 180 patients who had received irradiated plasma, 12.8% later had hepatitis.[78] In another study, the percentage was 7.6. Obviously irradiation is not a reliable method to sterilize plasma.[79]

Human thrombin used for hemostasis in surgical practice contained the virus of hepatitis, which caused disease in a number of victims. Bovine thrombin is a safer agent.[80]

‡ References 72 and 73.

Brick discusses the difficulties arising about liability and in awarding compensation for disability incurred during military service in personnel who were vaccinated 10 years ago with icterogenic yellow fever vaccine. Fifteen patients with chronic hepatic disease in 1952 who had been vaccinated in 1942 were studied. Eight had not had recognizable hepatitis or jaundice after the usual "incubation" period.[81] The question is, is hepatic disease now present related to vaccination 10 years ago? The incidence of cirrhosis after viral hepatitis is not yet known but perhaps is very small. Study of the liver in 43 cases of posthepatic cirrhosis revealed occasional instances in which the changes resembled those of Laennec's cirrhosis. Generally there was a difference. Postviral cirrhosis occurred in a younger age group, more often in females; there was a smaller incidence of ascites and greater incidence of jaundice as early symptoms; there was leucopenia, and the course was relentless and rapid.[82]

A study was made of 46 families in which one member had hepatitis. In 17 families, gamma globulin was given to other exposed members of the household and only one case of hepatitis developed. In the 29 untreated families secondary cases appeared in 14 persons, none among adults.[83]

Information derived from three essays in the June issue of the *Annals of Internal Medicine* does not favor the routine use of corticotropin or cortisone in the treatment of viral hepatitis. Striking benefit sometimes occurs, and the intensity of jaundice usually lessens more quickly than in untreated patients, but a relapse rate of 25%, the frequency of side-reactions, the failure to prevent chronic hepatitis, and the inability to stem the course of fulminant hepatitis does not favor the use of hormonal therapy.

In a study of 452 soldiers with viral hepatitis, strict bed-rest in contrast with optional rest had no effect on the speed of recovery. Patients who ate large prescribed amounts of protein and fat recovered a week sooner than those who selected their own food. Relapse occurred in 5% of patients regardless of the therapeutic procedures.[84]

The virus of herpes simplex was thought to have been the cause of hepatitis and encephalitis in twins who died within two weeks of birth. Eosinophilic or basophilic intranuclear inclusions and areas of necrosis were present in the liver.[85] Hypersensitivity to *p*-aminosalicylic acid used in the treatment of tuberculosis may cause symptoms easily confused with hepatitis or mononucleosis. Evidence of hepatic injury, atypical lymphocytes as high as 20%, and neutropenia may occur.[86]

Attempts failed to transmit the virus of hepatitis to mice previously treated with urethan, cortisone, corticotropin, and roentgen radiation. A transmissible form of hepatitis, probably a natural infection of mice, was encountered. Perhaps it may serve as a useful virus for further studies of hepatitis.[87]

Poliomyelitis.—A final report of controlled field studies of the use of gamma globulin for the prevention of poliomyelitis has been made. Gamma globulin modifies the severity of the disease if it develops within a week after injection. During the next four weeks a high though not complete degree of protection is afforded. Thereafter, immunity wanes and disappears after the eighth week. The authors discuss the value of the procedure and cite the great monetary cost involved. Gamma globulin is not a satisfactory method of prevention; a reliable vaccine would be preferable. Disadvantages are the short duration of passive protection,

the need of reinjection each time poliomyelitis appears in a community, the inability to determine the optimal dose, and inability to distinguish immune children from susceptible ones who need protection, and protection is not always complete.[88] In another paper, Hammon, to prevent wastage, outlines the circumstances, especially in family groups, under which gamma globulin should be used. Indiscriminate mass immunization is not recommended.[89]

According to British editorial comment, "passive immunization has never been satisfactory for the control of any infectious disease and will certainly not be the method of choice in poliomyelitis." [90] American editorial comment is similar. Little enthusiasm can be aroused by the evidence that gamma globulin prevents paralytic poliomyelitis. If paralysis recurs in only 1 in 100 or 1,000 cases of mild symptomless infection, the great numbers who would have to be protected makes the scheme impracticable.[91]

In regard to vaccination, children under 5 years of age develop neutralizing antibodies after the injection of formalin-inactivated poliomyelitis virus. The antibodies may persist for six months or more.[92] In a long paper, Salk reports preliminary results of trials with vaccine against poliomyelitis. Antibodies for all three types of virus were induced by polyvalent vaccine rendered innocuous by treatment with formaldehyde. The titers evoked were similar to those induced by natural infection. While the results are encouraging, many more studies will have to be made before vaccine can be recommended for practical use.[93] The matter was important enough to be the subject discussed by a committee of experts, who also recommend further study of the problem.[94] Large scale tests are in progress.

Koprowski and his associates fed living Type II (Lansing) poliomyelitis virus to 81 volunteers without apparent untoward effects. Virus was recovered from the stools of 29. Although viremia was not discovered in any, a rise in specific antibody titer was observed in most patients. In three no rise in antibody occurred above a prior low level. These may be considered as nonreactors.[95] Since minute amounts of virus given orally cause subclinical poliomyelitis, Sabin fed small doses to monkeys daily for several months. Inapparent infection occurred in most of them, and antibodies developed in 60%. Those with antibodies resisted subsequent infection with large doses of virus. Even those in whom antibodies were not demonstrable were more resistant to infection than were control animals. The results indicate one of the mechanisms, namely, repeated subinfectious doses, by which populations with low standards of hygiene may acquire a high degree of immunity and a relatively low incidence of paralysis if infection occurs.[96]

Viremia occurs in abortive cases and is followed by a high level of homologous antibody in two to four weeks. In one case, a dose of gamma globulin did not affect the antibody response.[97] Antibody in high level may persist for three years in persons who have had paralytic infection caused by Type I (Brunhilde) virus.[98]

Bodian reviews the pathogenesis of poliomyelitis in the light of recent discoveries. If the early presence of viremia is constant, it is assumed that in the majority of cases the disease is inapparent or mild. In rare instances, virus penetrates the central nervous system and causes disease. Penetration may be favored by seasonal factors, physical activity, pregnancy, trauma, or other circumstances which alter vascular permeability. He deplores the indiscriminate use of gamma globulin as hampering attempts to discover if immunoprophylaxis ever is possible. Much more must be known before vaccination can be properly applied.[99]

All three types of poliomyelitis virus can be studied after adapting them to mice, which greatly simplifies experimental procedures.[100] Testicular tissue obtained from immune monkeys supports the growth of poliomyelitis virus.[101] In attempts to isolate poliomyelitis virus from stools by means of tissue culture, 10 other infectious agents were encountered. Some behaved like Coxsackie viruses, and others could not be identified.[102] Mack virus, a newly recognized agent, was isolated from the feces of a sick child during an epidemic of poliomyelitis. It is not related to poliomyelitis virus, and specific neutralizing antibodies against it were demonstrable in the patient's blood. The virus may have caused the patient's disease.[103]

Although the first recorded epidemic of poliomyelitis in Tahiti occurred in 1951, the epidemic was unusual in that the peak of incidence occurred in the 10 to 19-year age group, not in young children. Subsequent studies revealed antibodies for all three types of virus in over 80% of persons over 5 years old. Obviously, unrecognized poliomyelitis had long been prevalent.[104]

During an epidemic of poliomyelitis in Ohio, members of a family without known contact with a patient were affected by a mild short illness. One child had sore throat, headache, and anorexia; one had headache and vomiting; one vomited, and the fourth had no symptoms. None was sick more than three or four days, and none developed paralysis. The virus of poliomyelitis was cultivated from the pharynx, the stool, and the blood from each of the four children.[105] The unusual occurrence of four fatal cases of bulbar poliomyelitis almost at once in another family of six children was ascribed to unusual familial susceptibility.[106]

Grant records 13 instances of "postinoculation" poliomyelitis after the injection of diphtheria toxoid or pertussis vaccine. The relationship in a few cases appeared to be coincidental, but in others intervals of 10 to 18 days between injection and onset of symptoms of poliomyelitis left no doubt in the author's mind of a causal relation.[107] According to Sartwell's observation, the incubation period of poliomyelitis ranges from 7 to 20 days, an average of 12.[108]

Coxsackie Disease.—Epidemic diseases of varied form associated with and probably caused by viruses of the Coxsackie group were reported from widely scattered places. There is question as to whether herpangina and pleurodynia, diseases of widely different clinical manifestations, are caused by the same or by different varieties of Coxsackie virus. Viruses so far isolated from patients with the diseases are serologically distinct, but their size and sedimentation constants are the same.[109] Other ailments, called summer influenza and myalgic meningitis, caused by Coxsackie virus A_2 were observed in Germany.[110] Epidemics caused by Type B virus occurred in England[111] and in South Africa. Young children were involved chiefly in familial outbreaks or in isolated instances. Meningitis, orchitis, and relapses were observed.[112]

An outbreak of over 100 cases of pleurodynia occurred in Texas between July and October, 1951. Until the disease was recognized, patients were thought to have herpes zoster, coronary occlusion, peptic ulcer, and cholecystitis. Coxsackie Type B virus was present in the stools in 16 of 17 patients.[113] Four papers on Coxsackie virus appeared in the February, 1953, issue of the *Australian Journal of Experimental Biology and Medical Science*. The virus was associated with an outbreak of poliomyelitis and, in another instance, with encephalitis. In the latter, it was

not isolated from the central nervous system, but specific antibodies were present against a newly classified strain, Type C, in the serum of all patients.

Encephalitis.—The following figures, collected in England, show the frequency of common diseases of childhood associated with 91 cases of "postinfectious" encephalitis: mumps, 37 cases; measles, 32; chickenpox, 9; influenza, 4; vaccinia, 2; rubella, 2; herpes, 2; pertussis, 2, and scarlet fever, 1. Four patients with measles and encephalitis died.[114] The problem of whether encephalitis is caused by the virus of the primary disease or is of other origin is unsettled.

An improvement seems to have been made in laboratory methods for the etiologic diagnosis of diseases grouped as aseptic meningitis. Not long ago less than 10% of cases could be diagnosed accurately. In a recent report, diagnosis was made in 25% of 854 sporadic cases in an 11-year period. About 12% were cases of mumps, and 9% were lymphocytic choriomeningitis. Since 1950 leptospires accounted for 7% and the virus of herpes simplex for 5%.[115] Similar figures are reported in England.[52]

Applebaum and his associates report on 50 cases of varicella encephalitis. The onset of symptoms occurs between the third and eighth day of the posteruptive stage. The course is variable, and the mortality rate is 5%. Sequels are rare. No treatment is effective.[116] Of 6,774 cases of varicella, encephalitis was diagnosed in 18, or in 0.21%. It is less common and less severe than the encephalitis of measles. In a study of the latter, of 77 patients, 22 died. Of 55 survivors who were followed, 22 had recovered completely.[117] Schildknecht recalls the fact that lymphocytic choriomeningitis is a systemic disease and may affect the kidneys, liver, and skin.[118]

A report was made of an epidemic of over 100 cases of meningoencephalitis during the summer of 1951. Nonparalytic poliomyelitis was suspected, because there were some paralytic cases. The symptoms lasted up to two weeks, with headache, vomiting, diplopia, delirium, or stupor. Pleocytosis of the spinal fluid usually occurred. All recovered. Coxsackie virus was isolated from one patient. It is uncertain if the virus caused the epidemic. Tests for lymphocytic choriomeningitis, mumps, and leptospirosis gave negative results.[119]

A newly recognized virus has been isolated from mosquitoes in California. Serologic studies suggest that it may have caused encephalitis in patients.[120] At the Fifth International Congress on Tropical Medicine, in Istanbul, Dick reported the existence of three more newly recognized neurotropic viruses in Africa, namely, Utaya, Uganda, and Zika. Mengo virus, like that of lymphocytic choriomeningitis, may be a natural infection of rodents.

Measles.—Measles was introduced apparently for the first time in Greenland in 1951 and was thus implanted on "virgin soil" in an unimmune population. The source was a recently arrived visitor who attended a dance at the onset of his symptoms. Within three months there were 4,221 cases and 36 doubtful attacks. The attack rate is said to have been 999 per 1,000, an unprecedented record. Seventy-two deaths (18 per 1,000) occurred. The incubation period averaged 13 to 14 days but extended from 6 to 19 days. Seroprophylaxis was given to 1,000 persons. Complications occurred in 45% of 1,157 patients not immunized; of these, 80% were early pneumonias during the first two days of eruption. The most serious complication was circulatory failure in elderly patients and in pregnant women.

Encephalitis occurred in six patients, and four died. No congenital anomalies were observed in infants born of mothers who had measles. The number of cases of tuberculosis increased, as though measles were responsible.§

Mumps.—The term epidemic parotitis should not replace the term mumps. Mumps is a systemic disease not confined to the parotid glands. A 48-year-old man had three recurrences of mumps with orchitis within three years.[123] In one outbreak about 25% of patients had encephalitis. Treatment, including drainage of spinal fluid, was ineffective. There was no relation between the severity of the illness and the number of cells in the spinal fluid.[124]

A skin-test for mumps using heat-inactivated virus is of value in diagnosis. In the case of swelling of the parotid gland not caused by mumps, the test will give a positive result of immunity. In the case of mumps affecting some other organs, the test will be negative at first and positive later as immunity develops. If the skin reacts positively in exposed persons, they are apparently immune and will not contract the disease.[125]

Hamsters develop bronchitis and pneumonia when inoculated intranasally with mumps virus from throat washings of patients. Complement-fixing antibodies appear in the blood.[126]

Rubella.—Attempt was made to devise a satisfactory method to immunize girls against rubella before the child-bearing age. Infection was transmitted to volunteers by inoculating serum or nasopharyngeal secretion obtained from a patient during the first day of the rash. Most volunteers were infected. The incubation period averaged 12 days. In some cases the disease was "typical," that is, as it is described in books; in others no rash appeared and the discomfort was minimal. Question arose whether inapparent rubella infection could give rise to congenital deformities in the fetus of an infected mother.[127]

Smallpox.—Despite the control of secondary pyogenic infection with penicillin, smallpox still is a serious disease. In a group of 21 patients in Korea, 40% died. The disease attacked chiefly persons in whom smallpox vaccine never was successful or those whose vaccination failed to "take" after a primary vaccination in childhood.[128]

Twenty-seven cases of neurologic disorders were observed after vaccination against smallpox. Death occurred in eight within hours or days after the onset. Encephalitis occurred in 16. In those who recovered, serious residual signs usually disappeared. Among 1,750,000 persons in the Armed Forces vaccinated between 1941 and 1950, only 10 developed postvaccinal encephalitis. Mild cases may have been missed.[129]

A woman vaccinated in the third month of pregnancy developed a severe primary reaction. Three months later there was premature birth of an infant, who soon died of vaccinia. Studies were then made of 203 vaccinated pregnant women, and a significant increase in mortality of fetuses was discovered if vaccination took place in the first trimester. Vaccination in this stage should be avoided.[130]

According to McCarthy and Downie, the isolation of virus from a patient is the only reliable laboratory method of distinguishing smallpox and alastrim from generalized vaccinia. The distinction between smallpox and alastrim rests on clinical

§ References 121 and 122.

and epidemiologic grounds.[131] In a case regarded as herpes zoster, lesions with intranuclear inclusions were found at necropsy in the skin, esophageal mucosa, myenteric plexus of the stomach, dorsal root ganglia, pancreas, adrenals, and elsewhere. The lesions and their distribution resembled those of varicella.[132] Weller reports the isolation and propagation in tissue cultures of filtrable agents from patients with varicella and with herpes zoster. The agents cause intranuclear inclusion bodies in inoculated tissues. The agents may be the causes of the respective diseases, but this relationship still is unproved.[133]

Rabies.—Thirty-two persons were bitten by a rabid wolf in Persia. Of 26 who received no antirabic treatment 13 did not develop rabies; the others died. The incubation period varied from 24 to 45 days. Severe lacerations do not always lead to death.[134] Hamsters inoculated with rabies virus develop many large Negri bodies and are better than mice for use in diagnostic procedures.[135]

Viral Dysentery.—Gordon and his co-workers continued their studies on this disease, which occurs in large epidemics and in sporadic or localized form in families as an endemic infection. The early results of Reimann were confirmed as regards the fecal-oral route of infection with a filtrable agent, but inhalation experiments failed. Japanese investigators, however, did transmit the disease by means of inhalation of nebulized stools. Evidence indicates that at least two filtrable agents are responsible; one causes afebrile disease, mild constitutional symptoms, and profuse watery stools and lasts about 96 hours; the other causes fever, constitutional symptoms, severe headache, and infrequent normal or loose stools and lasts only 24 hours.[136] No striking clinical-pathologic features were detected by Gordon,[137] but in my cases biopsy revealed infiltration of plasma cells and polymorphonuclear leucocytes in the rectal mucosa.[138] Whether the cellular reaction was evidence of infection or of irritation from diarrhea was not decided.

There is evidence of still other varieties. In some epidemics symptoms of involvement of the respiratory tract are prominent, and in these inhalation may be the mode of infection. In other outbreaks, like ones recently observed in England, nausea is the predominant symptom.[139]

Infectious Mononucleosis.—Observations have been made on the effect of infectious mononucleosis on different organs. Biopsy of the liver in 10 cases from 2 to 225 days after the onset showed lesions similar to those of viral hepatitis. Degenerative and regenerative changes were evident after seven months. The degree of histologic change was not in relation to abnormalities in tests of function of the liver.[140] Although the myocardium may be involved as well, the danger of serious trouble is minimal and changes in the electrocardiogram should cause no alarm.[141] In two patients the symptoms of acute pericarditis early in the disease obscured the diagnosis. It is necessary, therefore, to consider infectious mononucleosis as a cause in instances of so-called idiopathic benign or viral pericarditis.‖ Three patients with infectious mononucleosis developed the Guillain-Barré syndrome.¶

In spite of a number of earlier reports of success, there is no acceptable evidence of any beneficial effect of antibiotic therapy on the course of the disease. In Walker's 78 patients, neither chloramphenicol nor chlortetracycline had any influence.[146]

‖ References 142 and 143.
¶ References 144 and 145.

Newcastle Disease.—Five cases of Newcastle disease have been described. The chief features are malaise, conjunctivitis, ulcers in the oral mucosa, and preauricular lymphadenopathy. The incubation period appears to be 18 to 24 hours. The virus was isolated from nasal, conjunctival, and oral secretions and urine.[147]

Moolten and his associates isolated the virus of Newcastle disease from three patients with hemolytic anemia and isolated several relatively innocuous viruses from patients with other diseases. Suggestion is made that, if they are not the cause, hemagglutinative and hemolyzing viruses at least may play a part in certain hematologic and vascular changes.[148] Influenza virus shortens the life span of erythrocytes, but its relation to the cause of hemolytic anemia is not clear.[149]

Reiter's Disease—Trachoma.—The cause of Reiter's disease still is unknown. In a series of 23 cases, there was no evidence of previous attacks of shigellosis. The skin and oral mucous membrane often were involved besides the urethra, the eyes, and the joints. The lesions resemble those of keratoderma blennorrhagica. Bacterial culture studies were unrewarding. Antibiotic therapy had no influence on the disease. It appears to be a venereal viral infection, and the urethra may be the portal of entry.[150]

Even the nature of trachoma is unsettled. It has been suggested previously that inclusion blennorrhea in which the urethral and nasal mucous membranes are involved is identical with trachoma. Evidence in favor of this view is presented. Inclusion bodies similar to those found in the trachomatous conjunctiva were reported in the nasal and urethral mucosa. Symptoms of rhinitis may accompany the onset of trachoma, but urethritis was not observed.[151] If these are inclusions and actually represent aggregates of elementary bodies of trachoma, trachoma may be a general disease of the mucosal surfaces and is not limited to the eye. Such inclusions, however, may be confused with degenerated leucocytes or may be unrelated to trachoma. Further study is needed.

Epidemic Hemorrhagic Fever.—Report of a symposium on epidemic hemorrhagic fever among troops in Korea appeared in the January, 1953, issue of the *Annals of Internal Medicine*. Clinical studies of 55 cases of epidemic hemorrhagic fever were described elsewhere. The disease usually is severe, systemic, and hemorrhagic and involves the respiratory, urinary, and gastrointestinal tracts and the central nervous, cardiovascular, hematopoietic, and endocrine systems. Detailed studies are described.[152]

Other Diseases.—The common wart (verruca vulgaris) probably is viral in origin. A filtrable agent obtained from warts has been cultivated in the chick embryo.[153] A virus called Egypt 101 was inoculated into 34 patients with advanced neoplastic disease. The infection it caused had a transient inhibitory effect on the growth of the tumors. In 14 patients the virus localized in tumor tissue.[154] A new filtrable agent was discovered to cause carcinoma of the salivary gland in mice. Unfiltered extracts of organs caused leukemia. It is uncertain whether two separate agents are involved.[155] The fibroma virus of Shope was transmitted to rabbits by means of the bites of mosquitoes and fleas.[156] At a meeting of the Society for Investigative Dermatology, Meirowsky reported experiments suggesting that a type of basal cell carcinoma of the skin is caused by a filtrable agent.

An outbreak of mousepox of unknown source in a closely controlled colony of mice killed more than 50% of the animals over six to eight weeks. Attempts to limit the spread of infection were unsuccessful. The virus of the disease seems to be related to the virus of vaccina and causes the murine counterpart of human pox disease.#

McCrea and Duran-Reynals show that the virus-inactivating substance obtained from a component of hydrolized hyaluronic acid may be glycuronic acid or a glucuronide. The substance may interact with vaccinia virus, for example, in a way similar to its conjugating action in detoxicating mechanisms and may play a role in the mechanism of defense against infection.[159]

DISEASES CAUSED BY COCCI

Pneumonia.—The death-rate from "pneumonia and influenza" has dropped about 75% since 1936, when sulfonamide compounds were introduced. Yet diseases falling under this all-inclusive statistical heading accounted for over 50,000 deaths in the United States in 1951. As a cause of death, pneumonia is outranked only by cardiovascular renal diseases and cancer among policy holders of a life insurance company. Most deaths occur among the very young and the very old.[160] In a study of 8,000 cases, in England, the mortality from lobar pneumonia was reduced from 20% to 10% after 1938. The incidence of empyema fell from 4% to less than 1%. Surprisingly, the death rate from "bronchopneumonia" is almost unchanged by chemotherapy or penicillin therapy. Treatment with sulfonamide compounds gave results as good as or better than those with penicillin, especially in female patients.[161]

The possible relationship of minor respiratory tract infection and of pneumonia to bronchiectasis has been discussed.[162] A causal relationship indeed may exist, but other possibilities must be considered as well. One is that bronchiectasis may predispose patients to pneumonia. Another is that if a person has preexistant, asymptomatic, unrecognized bronchiectasis, any intercurrent pulmonary infection may be wrongly blamed as the primary cause.

Thirty-six children with bronchiectasis with Hemophilus influenza were treated with chloramphenicol. The results were not encouraging. Remission usually followed treatment, but only patients with mild disease seemed to derive lasting benefit. Death of one patient with aplastic anemia led the author to abandon treatment with chloramphenicol.[163]

According to previous studies, the variety of bacteria found in the sputum of patients with chronic bronchitis is similar to that found in the throat of healthy persons. In May's opinion, errors may result if only one portion of sputum is cultured. By making cultures from five parts of each sample, error is reduced. Pus in the sputum is significantly associated with pneumococci and Pfeiffer's bacilli. If antibiotic therapy removes these bacteria, pus diminishes in amount.[164] Sputum can be liquefied or homogenized by mixture with 1% pancreatin for better bacteriologic examination.[165]

Despite the wane of interest in the Pneumococcus, studies still are carried on. Phagocytosis and lymphatic drainage usually are held responsible for the rapid disposal of pneumococci in the lungs of mice. The bronchial cilia also are of importance in the rapid early elimination of the cocci.[166] In another study, pneumococci

References 157 and 158.

disappeared in animals treated with penicillin or chlortetracycline regardless of whether the leucocytes were destroyed with benzene or not.[167] Evidently phagocytosis is not of so great importance as many investigators believe.

It is possible by infrared spectrophotometry to identify pneumococcic polysaccharides according to their type. The spectrographic characteristics of some are distinctive; others are similar and indistinguishable.[168]

Streptococcic Disease.—Several studies of "epidemics" of nephritis in the past decade were not mentioned in these reviews because of etiologic uncertainty. A case in point is a series of instances of nephritis observed in a local area within a few months.[169] Other outbreaks of nephritis affecting several members of family groups suggest a common cause, perhaps a single type of Streptococcus. Evidently, as subsequent studies have shown, Type 12 hemolytic streptococci are particularly nephritogenic. The subject of the epidemiology of streptococcic infection in relation to acute nephritis and to rheumatic fever has been reviewed.[170]

During an epidemic of 400 cases of streptococcic pharyngitis, nephritis did not occur in any of 113 cases in which streptococci of Types 3, 6 and 19 were the cause. Nephritis developed in 15 of 191 patients infected with Type 12 streptococci about 10 days after the sore throat.[171] In another study, Type 12 streptococci caused 84% of cases of nephritis.[172] Type 12 streptococci were isolated from half of a group of 39 infants with nephritis.[173] There were, on the other hand, epidemics caused by Type 12 streptococci in which the incidence of nephritis was low. There seem to be differences among Type 12 strains; some may be strongly nephritogenic, others not.

An outbreak of 25 cases of infection with hemolytic streptococci occurred in a maternity hospital. The majority of strains were of Type 13. Most of them were resistant to sulfadiazine but were sensitive to penicillin. The outbreak began with a nurse who had a sore throat. In succession, other infections, such as erysipelas, sore throat, and genitourinary tract infection, appeared. The response to penicillin in severe cases was slow.[174]

In the dosage used, penicillin, chlortetracycline, and oxytetracycline seemed equally able to shorten the duration of symptoms of hemolytic streptococcic pharyngitis as compared with the duration in untreated patients. Therapy also suppressed the development of antibodies.[175] One wonders if doses as large as 600,000 units of penicillin daily for five days are necessary to control a usually mild disease. By using a special procedure, beta hemolytic streptococci were induced to become resistant to streptomycin, chlortetracycline, and bacitracin but not to penicillin.[176]

Patients who had developed a high antistreptolysin titer after infection with Type 19 streptococci were not resistant to reinfection with streptococci of Type 17 several weeks later. Apparently, immunity to streptococci is type-specific and antistreptolysin does not confer immunity.[177]

Mice immunized against Group A streptococci and nonimmunized mice were inoculated with Group A streptococci and treated with a small fraction of the normally curative dose of penicillin. Nonimmune mice all died, but penicillin sufficed to reduce the bacterial population in immunized mice so that the cocci could be disposed of by defenses of the host.[178] A convenient method for experimental purposes is described by which infection of cervical lymph nodes with hemolytic streptococci may be caused by the intranasal inoculation of mice.[179]

Dienes isolated so-called L cultures from only two of many strains of alpha and beta hemolytic streptococci obtained from the throat and genitalia. They were similar to those which appeared on direct culture from areas of the throat where penicillin inhibited other bacterial growth.[180] The use of the designation "L" is confusing, and the significance of the small colonies is unknown. A pleuropneumonia-like bacterium found in the blood and cervical secretions of a patient raised the question whether it was pathogenic or a commensal.[181]

Rheumatism.—The Tenth Rheumatism Review, covering publications from 1946 to 1950, was published in the September and October, 1953, issues of the *Annals of Internal Medicine.* Over 2,200 references are collected and discussed on 269 pages.

Rheumatic Fever.—Modern methods of controlling infection with hemolytic streptococci are not wholly responsible for reducing the death rate of rheumatic fever and cardiac disease to a fifth of what it was in 1911. There has been a steady decline in the mortality rate since then, owing to general improvement in the health of children. However, a reduction of the death rate by half since 1940, is, no doubt, largely due to antistreptococcic therapy. Despite the gain, rheumatic fever and rheumatic lesions cause more deaths than any other disease at ages 15 to 19.[182]

None of the tests now used for the diagnosis of rheumatic fever is entirely satisfactory. Since measurement of the amount of antistreptolysin O gives information in respect to a previous infection with hemolytic streptococci, it is regarded as a semispecific test. Most victims of streptococcic infection develop antistreptolysin, but only a small per cent of them acquire rheumatic fever. Other tests are nonspecific, as, for example, the sedimentation rate of erythrocytes, the leucocyte count, and the measurement of C-reactive protein. All these reactions tend to revert to normal when rheumatic symptoms are suppressed by therapy, even though, as many believe, the underlying disease persists.[183] On the other hand, according to others, therapy with salicylates may do more than merely mask the clinical manifestations. It may suppress the inflammation. If so, treatment should be continued for months.[184]

In a controlled study, cortisone or corticotropin caused prompt clinical improvement in the extracardiac manifestations of acute rheumatic fever. In some cases, therapy may be life saving. Abnormal results of laboratory tests may return to normal in a few weeks. However, rheumatic activity persisted in about half of the patients after therapy. It is not known if therapy has any influence on injury to the heart. Murmurs usually persist, and an enlarged heart rarely returns to its normal size after treatment. Hormonal therapy is recommended in rapidly progressive forms of rheumatic fever when systemic involvement is severe.[185]

Miller and his associates were unable to show that persons with rheumatic fever respond in a peculiar way to antigens other than to that of the hemolytic Streptococcus. The immune response to influenza vaccine and to typhoid vaccine was as variable in patients convalescent from rheumatic fever as in nonrheumatic ones.[186]

Treatment with penicillin within five days after the onset of symptoms of streptococcic pharyngitis results in 40% suppression of antistreptolysin. If this immune reaction indicates a parallel suppression of the subsequent response on which the onset of rheumatic fever depends, early treatment is desirable.[187]

One of the few circumstances in which preparations of repository penicillin are of use is in the prevention of hemolytic streptococcic infection to prevent rheumatic fever. Benzathine penicillin B (Bicillin), when injected once monthly, may serve as a useful prophylactic agent. Hypersensitive reactions occur.[188]

Methods for the protection of patients with rheumatic fever, for the prevention of rheumatic fever, and for the treatment of hemolytic streptococcic infections are outlined conveniently in statements of the American Heart Association [189] and by others.[190]

Focal Infection.—While the theory of focal infection pertaining to teeth and tonsils and systemic disease is not abused as much as it was in the past, there are physicians of the older generation who still subscribe to the last remnants of this idea. In 1953 one still writes that "focal infection may cause such effects as general debility, fatigue, malaise, anorexia, headache, excessive drowsiness, anemia, loss of weight, hypertension and reduced immunologic responses." [191] What evidence supports such a statement? An extensive study sponsored by the Council of Dental Health is cited, but the conclusions of the committee are not. Furthermore, the same gamut of diseases, most of them of unknown cause, which were under consideration 30 years ago is listed as possibly due to focal infection. Solicited information from two consultants advises the removal of foci of infection in teeth and tonsils to lessen the pains of tabes dorsalis.[192] It is notable that recent publications on the subject have nothing more than personal opinions, philosophic discussions, references to previous publications, and aphorisms to offer in support of their views.* No direct observations, controlled or otherwise, show a connection between foci of infection in teeth or tonsils with the diseases mentioned. Tonsillectomy is not without serious risks.[195]

In pertinent correspondence, the Rowes reaffirm the view of most allergists that infection is not an important cause of clinical allergy. Foods and inhaled substances are far more important.[196] Realization of these facts will obviate much unnecessary oral and nasal surgery.

Staphylococcic Disease.—The bacteriophage method of separating strains of staphylococci into types or groups gives no more information than Cowan's serologic method. There are three main groups. Nevertheless, with the technique used no particular kinds of staphylococci were found to be unduly common in any disease but for two exceptions. In staphylococcic pneumonia, Group I strains are predominant. Not all strains associated with the fulminating disease are penicillin-resistant. In food poisoning, Group III staphylococci are found almost exclusively. The same group, significantly, is commonest in the feces of normal persons.[197] Bacteriophage typing of staphylococci still is not adaptable to routine usage in most laboratories; however, it is useful in tracing epidemics. Six broad phage types are established. Of 290 strains about half could be classified.[198]

Like pneumococci, staphylococci, when present, are not always the cause of disease and many are not typable. In frank staphylococcic infections, a larger proportion of strains can be typed. There was found to be a predominance of Group II strains in abscesses and osteomyelitis caused by penicillin-sensitive strains. Group III strains comprised about 80% of penicillin-resistant strains.[199]

* References 193 and 194.

Three cases of staphylococcic scarlet fever caused by a toxin-producing Staphylococcus have been described.[200]

Meningitis.—Haworth calls attention to the continued high mortality rate in infants with meningitis. Of 288 deaths from meningococcic infection, 112 were in infants under one year of age. A factor in this high death rate is delay in diagnosis. The typical symptoms and signs are absent or delayed in 26% of young infants. Diagnostic lumbar puncture should not await the development of frank evidence of meningitis.[201]

The serologic demonstration and measurement of agglutinin for meningococci is a reliable test for diagnosis, for typing of the causative meningococcus, and for tracing the source of an outbreak of meningitis. The test is less laborious than isolating and typing meningococci. Samples of serum may be preserved for later study. A positive test may reveal asymptomatic nasopharyngeal meningococcic infection.[202]

If one excludes three cases in which death occurred within 24 hours after treatment, the mortality rate among 28 cases of pneumococcic meningitis was zero, a remarkable achievement. Patients received 1,600,000 to 4,000,000 units of penicillin intramuscularly and 25,000 units intrathecally daily.[203] A fatal case of meningitis was described in which Mycobacterium tuberculosis, Neisseria meningitidis, and alpha hemolytic Streptococcus were present. The patient had pulmonary tuberculosis and endocarditis.[204]

Detailed plans of therapy for various forms of bacterial meningitis are outlined by Alexander.[205]

DISEASES CAUSED BY BACILLI

Tuberculosis.—For the first time, the death rate from tuberculosis last year fell below 20 per 100,000 among policy holders of a life-insurance company in the United States. The death rate has fallen nearly 90% in the past 40 years. On the other hand, in certain regions where a fairly complete census is kept there is little evidence of a decline in the number of cases.[206] The decline in the number of persons whose skin reacts to tuberculin suggests a decline in morbidity parallel to but not so great as the decline in mortality. It is estimated that there are now 1,200,000 cases of tuberculosis in the United States, and, of these, 400,000 are active.

Modern methods of treatment in the past 15 years have caused a change in the kind of tuberculous patients studied in hospitals. They tend to be older, and a smaller proportion have far-advanced disease. The average length of hospitalization has increased, and the mortality rate has decreased. The need for more hospital beds, surprisingly, has increased.[207]

A study of 99 patients with pulmonary tuberculosis confirmed the view that combined therapy at present is the most satisfactory method of treatment. Patients received 150 or 300 mg. of isoniazid daily and 2 gm. of streptomycin every third day. Toxicity seldom occurred, and bacterial resistance was minimal after four months. Treatment should be continued for three to six months. Bed rest, collapse measures, and excisional surgery still are needed. Cavitation was present in 37% after months of treatment. Relapse may occur afterward.[208]

From a series of studies, a British committee reports beneficial effects after a three-month period of treatment with a combination of *p*-aminosalicylic acid (sodium) 20 gm. daily and isoniazid 200 mg. daily. The results were as good as

those from streptomycin alone or combined with isoniazid.[209] Crofton describes a method to desensitize patients under treatment and persons who handle streptomycin and *p*-aminosalicylic acid who have become hypersensitive to the drugs. Small but increasing amounts of the respective drugs are injected intramuscularly.[210]

Treatment of tuberculous meningitis with orally administered isoniazid alone or combined with streptomycin has given favorable results.[211] Of 100 patients in Spain treated with combined drugs, 94 recovered and only 7 had significant sequels.[212] The results as reported are far better than those previously reported anywhere and must be regarded skeptically.

Experimentally induced meningeal tuberculosis in guinea pigs was controlled by the intramuscular injection of streptomycin in doses of 30 mg. daily.[213] A patient with tuberculous pericarditis developed tuberculous meningitis while under treatment with streptomycin.[214]

Isoniazid is said to be superior to streptomycin for the treatment of meningitis but less effective for caseocavernous pulmonary or extrapulmonary tuberculosis. Some lesions resolve, while others progress during therapy.[215] According to others, only noncavitary minimal lesions are suitable for medical treatment alone. Surgical excision of cavitary, caseonodose, and caseopneumonic lesions and tuberculomas gave good results and permitted 93% of 221 patients to recover quickly.[216] On the other hand, tuberculomas may remain quiescent for many years without surgical or antibiotic therapy. In a study of 38 patients, 34 were well 20 years later. Neoplasm must be ruled out.[217]

Unfortunately, isoniazid at times may cause tingling, paresthesia, weakness, and paralysis of the extremities. Symptoms usually disappear when treatment is stopped.[218] Paraaminosalicylic acid may cause toxic hepatitis.

According to Corper, no therapeutic agent by itself can eliminate tubercle bacilli from the body in a reasonable time. While streptomycin and related compounds and isoniazid and its homologues are valuable therapeutic agents, they are only temporary retardants. Tubercle bacilli may become resistant to both.[219] McCune's study in mice showed that both streptomycin and isoniazid, alone or combined, had no influence on the persistence of tubercle bacilli in the spleen, despite 90 days of intensive therapy. Bacteria persisted regardless of whether they developed resistance to the drugs.[220] Streptomycin inhibits the growth of tubercle bacilli located intracellularly in macrophages in tissue culture, but the amount necessary is more than can be achieved in body fluids during therapy. Most of the new antituberculous drugs are effective against intracellular tubercle bacilli.[221]

Studies on rabbits show that genetics plays an important role in resistance against tuberculosis. A highly resistant and a highly susceptible strain were cross bred. Among the hybrids there was evidence of intermediate resistance, as expected. Back cross of hybrids to resistant ancestors yielded offspring which again were resistant to infection with tubercle bacilli. Back cross of hybrids to susceptible ancestors brought about descendants in whom resistance was greater than in the original susceptibles.[222]

Leprosy.—Tuberculosis often complicates leprosy. At the Carville Leprosarium 141 of 607 patients who died had tuberculosis at the time of death. Another 16 had minimal active tuberculosis, and 13 had arrested tuberculosis. Sulfone therapy has reduced the death rate.[223] Isoniazid does not seem to be of value in the treatment of leprosy.[224]

Typhoid.—Of 657 men in Egypt who received antityphoid vaccine, 84 contracted typhoid caused by bacilli of phage-type J. In a second outbreak, two months later, 235 of 688 men were infected by phage-type E-1 bacilli. Food handlers probably were the source. Of 54 men who had typhoid in the first epidemic, 11 again contracted the disease. Second attacks of the disease occur because the immunity conferred by an attack and by vaccination is not solid or durable.[225]

Chloramphenicol was given to 398 patients with typhoid. Dosage of 12.5 mg. per kilogram of body weight, given twice daily, was satisfactory. Persistence of treatment for 12 days after defervescence reduced the relapse rate to 3.9%, in contrast with 26% after only three days of convalescent therapy. If chloramphenicol cannot be given orally, intramuscular injection in solution in acetyl-dimethylamine is advised.[226]

The source of an epidemic of typhoid in Australia was traced to a commercial brand of contaminated dried coconut.[227]

Cholera.—The puzzle as to where the source of cholera resides during interepidemic periods is unsolved. Pollitzer reviewed reports of investigators after 1935, who showed that convalescent carriers rarely excrete vibrios a month later.[228] Evidence purporting to incriminate carriers as sources is not complete.[229] Yet there is no other reasonable assumption at present besides the existence of carriers in whom Vibrio comma may reside in an unrecognizable or undetectable variant form.

Plague.—It is said that, despite sulfonamide therapy, the mortality rate of pneumonic plague up to 1948 was nearly 100%. It is doubtful, however, even in untreated patients, whether the mortality actually is so high. Streptomycin is an effective therapeutic agent, but chloramphenicol and oxytetracycline were used in eight cases, with curative effects in seven. Treatment must be started within the first 24 hours to be of value. Cortisone added to the treatment did not give the favorable effects noted when it is used in the treatment of typhoid.[230]

Diphtheria.—An epidemic of 58 cases of diphtheria, with 6 deaths, occurred in an English community of 233,000 persons. Infection seemed to have been spread mainly at home rather than in schools. The incidence fell immediately after mass immunization.[231]

Diphtheroid bacilli or corynebacteria other than diphtheria bacilli occasionally are present in the blood, as detected by culture. In 27 instances, bacteremia occurred in patients with lymphomatous disease.[232] Diphtheroids at one time were suspected as being the cause of Hodgkin's disease.

Brucellosis.—The diagnosis of brucellosis rests on epidemiologic and clinical facts, the agglutination test, and the blood culture. Only the last is decisive. In a series of 35 cases, blood culture was positive in each, and in each the agglutinin titer rose to between 1 : 160 and 1 : 5,120. However, clear-cut symptoms, fever, lymphadenopathy, loss of weight, splenomegaly, and hepatomegaly seldom were noted. Chlortetracycline alone, in doses of 2 gm. daily for 7 to 21 days, was the most satisfactory form of treatment.[233] Although corticotropin caused prompt improvement in one patient with acute brucellosis, Brucella abortus persisted in the blood. Therapy had no effect in patients with chronic brucellosis. There is little or no need for using either cortisone or corticotropin.[234] Cases of chronic brucellosis are discussed by Barrett and Rickards.[235]

According to Hall and Manion, the tube-dilution method, as devised by Wright over 50 years ago, is the most reliable test for Brucella agglutinin. It is more sensitive than Huddleston's rapid microscopic slide test. Castaneda's procedure is useful as a quick bedside test.[236]

Views on the accepted diagnostic and therapeutic procedures for brucellosis have been published by an international committee.[237]

DISEASES CAUSED BY FUNGI

Histoplasmosis.—A study of epidemic outbreaks of histoplasmosis further favors the view that infection usually is air-borne and enters the respiratory tract in dust containing the spores. There is a relation between the number of pulmonary lesions and the severity of the illness on one hand and the length and intensity of exposure to the dust on the other. There is frequent association with animal excreta and with decayed wood and sawdust as sources and vectors of infection. Recovery from an attack is said to be followed by a degree of resistance to reinfection.[238]

In 120 cases of histoplasmosis, the central nervous system was affected in 10%. The involvement may mimic tuberculous meningitis.[239] Anorectal manifestations occur.[240] Since chronic histoplasmosis may be mistaken for chronic pulmonary tuberculosis, it will occasionally be encountered in patients subjected to therapeutic pulmonary surgery. Histoplasma capsulatum can be demonstrated in the tissues removed at biopsy or at operation.[241]

It was shown previously that routine cultures of bone marrow for the detection of H. capsulatum rarely revealed the fungus. Studies in infants and children in an endemic area (Indianapolis) yielded better results. Cultures were obtained in 5 instances out of 76. In two cases Histoplasma organisms were observed in the marrow. The histoplasmin skin test gave a negative result in two instances.[242]

A simple technique for the cultivation of H. capsulatum intracellularly in mouse tissue cells has been described. The method may be useful for the cultivation of other pathogens.[243]

Isoniazid gave encouraging results in the treatment of actinomycosis.[244] However, as one looks back, first the iodine salts, then the sulfonamides, penicillin, streptomycin, the broad-spectrum antibiotics, and now isoniazid gave "encouraging" results. Obviously, the ideal therapeutic agent is not yet discovered. Three patients with systemic blastomycosis were treated successfully with 2-hydroxystilbamidine.[245]

Uncritical therapeusis persists in regard to fungal diseases. Desensitization, large doses of potassium iodide, and the intravenous injection of gentian violet still are recommended for the treatment of moniliasis despite the lack of evidence, other than observations in a few cases, that any is of value.[246]

DISEASES CAUSED BY TREPONEMES AND LEPTOSPIRES

Syphilis.—Editorial comment emphasizes the great advances in recent years in the epidemiology, laboratory diagnosis, and treatment of syphilis. Although the disease, like other infections, has declined steadily in incidence for 100 years, regardless of preventive or therapeutic measures, the decline was precipitous after the use of penicillin. The great diminution in the number of fresh infections raises

the hope of reducing syphilis to an insignificant disease. After only 10 years of use penicillin has completely replaced the heavy metals compounds in therapy. Treatment now is shorter, cheaper, more efficient, and less dangerous. The matter of false-positive diagnostic serologic reactions is better understood. A new method, namely, the treponemal immobilization test (TPI) gives specific diagnostic information as to the presence or absence of syphilis. Among 300 seropositive patients suspected of having syphilis, the TPI test ruled out the disease in 45%. The TPI test, unfortunately, is a complicated one and can be done only in a few specially equipped laboratories. Simplified methods may be available soon.[247]

Moore and Mohr studied the problem of biologic false-positive reactions to present standard serologic tests for syphilis. Transient falsely positive reactions may be present during a number of diseases other than syphilis. Among 136 patients whose blood gave persistently false-positive reactions, 4 were eventually diagnosed as having lupus erythematosus disseminatus, 1 had rheumatoid arthritis, 1 had sarcoidosis, and 1 had Gaucher's disease. In 21 others, one of the so-called collagen diseases still is suspected as the cause. Evidently, persistence of a false-positive reaction for syphilis must be regarded seriously, and a cause for it should be sought.[248] Literature on syphilis is reviewed in the April and May, 1953, issues of this journal.

Leptospirosis.—At a meeting of the American Federation for Clinical Research, Williams and his co-workers reported an epidemic of leptospirosis in bathers who swam in a pool contaminated with Leptospira canicola. Twenty-six, or 47%, of exposed persons were sick. Infected cattle and swine had access to the pool. Leptospira pomona, previously reported among cattle in Australia and Europe, has been found in farm animals in Illinois.[249] Although, previously, clinical study indicated that antibiotics were of no value in the treatment of leptospiroses, a new one, erythromycin, might be effective, as suggested by studies in chick embryo cultures.[250]

The fact that two-day-old chicks inoculated with leptospires develop leptospiremia of five days' duration without clinical illness may be used as the basis of a method for the diagnostic isolation of leptospires.[251]

DISEASES CAUSED BY RICKETTSIA

Q Fever.—An explosive outbreak of Q fever was observed on a farm in England. Of 15 residents, all the adults and 1 child were sick, an attack rate of 100%. Of nine visitors to the farm three were infected. There was a wide variation in the degree of illness. The duration varied from a few days to seven weeks. Cows and pigs were suspected as the sources of infection.[252]

A study of the distribution of Q fever in England suggested that in some regions about 2% of the population had been infected. Probably many of the infections were inapparent and most of them were unrecognized. Only 69 cases are recorded, 58 of which resembled viral pneumonia. There were four deaths. Two-thirds were exposed to known sources of Q fever. About 8% of herds of cattle excreted Coxiella burneti in milk in one section of the country and 0.8% in another.[253]

Trench Fever.—Mooser and Weyer succeeded in establishing longlasting rickettsemia in monkeys inoculated with Rickettsia quintana. Infection was asymptomatic.[254]

DISEASES CAUSED BY PROTOZOA

Amebiasis.—The comparative value of various amebacides was tested. According to one group of investigators in Korea, oxytetracycline alone and in combination with emetine, carbarsone, chiniofon, and chloroquine phosphate caused excellent initial response and low relapse rates. Bismuth glycolylarsanilate (Milibis), chloroquine, and the combination of chlortetracycline and chloroquine phosphate also were effective. Even these methods need to be improved.[255] Sanchez Vegas, in Venezuela, treated 265 cases of amebiasis and observed them more than six months. The combination of bismuth glycolylarsanilate and chloroquine, in his opinion, gave the best results.[256]

Although therapy with chlortetracycline and oxytetracycline often is more quickly effective than the older amebacides in the treatment of acute amebic dysentery, relapses occur. It is suggested that these antibiotics suppress bacteria which favor the growth and invasiveness of amebas and, by so doing, control amebiasis temporarily. British physicians recommend the use of established amebacides together with the antibiotics mentioned.[257]

In a study of 50 patients with amebiasis, Weiser and his co-workers were disappointed with the therapeutic effect of antibiotics. The results of therapy with oxytetracycline were no better than those reported from less potentially toxic drugs. In three instances, therapy with oxytetracycline seemed to prolong diarrhea and staphylococci appeared in the stools. The results of therapy with chloroquine and emetine were variable; one drug was no better than the other. Apparently, in many previous enthusiastic therapeutic reports the studies were incomplete. Unless the mucosa is inspected by sigmoidoscopy and material is examined for ameba directly from the mucus, diagnosis is insecure and proof of cure is not established.[259]

By using a serologic technique like that for the treponemal immobilization test, a similar behavior of amebas can be shown. The serum of rabbits previously appropriately inoculated with Endameba histolytica and Trypanosoma cruzi causes immobilization and amebal trophozoites. The serum from some patients with amebiasis caused similar immobilization, but less vigorously. The reaction may prove to be of diagnostic value.[258]

Toxoplasmosis.—In a review of the knowledge of toxoplasmosis Sabin mentions a number of clinical conditions, such as encephalitis, chorioretinitis, retrolental fibroplasia, fever of unknown cause, lymphadenitis, and exanthems, which were suspected as being associated with Toxoplasma but without further evidence. Methods for diagnosis are outlined, which should be applied during the neonatal period when there are signs of encephalitis, rash, jaundice, hepatosplenomegaly with or without hydrocephalus, microcephaly, chorioretinopathy, and psychomotor retardation. Specimens for diagnosis may be sent to the Communicable Disease Center of the United States Public Health Service.[260]

A nonfatal case of toxoplasmosis was observed in an adult. Viral pneumonia and cat-scratch fever were suspected, but Toxoplasma organisms were cultivated from an enlarged axillary lymph node excised 53 days after the onset of illness.[261] Sexton and his co-workers report a fatal case of toxoplasmosis in a laboratory worker who had handled material infected with Toxoplasma. The organisms were present in the heart, spleen, liver, and spinal fluid.[262]

Beckett and Flynn had no difficulty in collecting 12 cases in the region between New York and Boston. Numerous unreported cases were observed. Toxoplasmosis may appear in these various forms: asymptomatic, as a grippe-like disease resembling infectious mononucleosis, as chorioretinitis, and as an acquired or congenital systemic infection. Dogs and cats may be sources of the disease.[263] Toxoplasmosis was discovered in cows in Ohio. Milk contained Toxoplasma and may serve as a vector.[264] Seven cases, one in an adult, were studied in Germany.[265] Various aspects of toxoplasmosis were reviewed in six papers in the May issue of the *American Journal of Tropical Medicine and Hygiene.*

Ophthalmologists are likely to encounter the disease. Organisms resembling Toxoplasma were found in chorioretinal lesions of 53 eyes in the registry of ophthalmic pathology. Among 131 eyes in which tuberculosis was diagnosed, Toxoplasma-like bodies were present in 30.[266]

Antibodies to Toxoplasma often are found in man and in various animals. According to Feldman, who made a survey in normal persons by employing the skin test, no positive reactions were demonstrated in children under four years of age in Cincinnati and New York, but there was a constant increase with age, until by middle-age half of those tested reacted to the antigen. A large proportion of cats, dogs, and guinea pigs also react positively to the antigen. The test as a diagnostic aid must therefore be interpreted with caution.[267]

MISCELLANEOUS CONSIDERATIONS

Sarcoidosis.—By transferring passive tuberculin sensitivity to tuberculin-negative patients with sarcoidosis, Urbach and his associates add further evidence that anergy to tuberculin in sarcoid disease is nonspecific and indicates no etiologic relation to tuberculosis.[268]

Similar granulomatous changes and clinical features in several diseases have led to diagnostic confusion. Several years ago I described the clinical and pathologic similarities and possible relationship between trichinosis and periarteritis (polyvasculitis) [269] and, more recently, a resemblance, at times, between histoplasmosis and sarcoidosis.[270] Jackson and Kass now suggest a possible relationship or identity of periarteritis and sarcoidosis. It is possible that both are manifestations of allergy and may be induced as end results by a variety of causes, infectious or otherwise. In one, the granulomas are chiefly vascular; in the other, extravascular.[271] It is unsafe, however, to assume identity on the basis of clinical and pathologic characters, because tissues in general have a limited ability to react.

Malaria.—Ten cases of malaria occurred among occupants of a summer camp in California. The source seemed to be in a Korean veteran who had a relapse of malaria while camping nearby.[272] Progress in the knowledge of malaria in the last decade was reviewed by Young.[273]

Paragonimiasis.—Owing to residual infection, pulmonary paragonimiasis may be encountered wherever there are veterans who served in endemic areas in World War II. The subject was reviewed and inaccuracies in older descriptions were corrected by military physicians. The infection, if unsuspected, may be mistaken for tuberculosis, bronchiectasis, or cystic disease of the lung. The chief clinical features are repeated hemoptysis, often for years, and surprisingly little systemic

disturbance, even though there may be localization in many other organs and tissues. Death from pulmonary infection alone was not observed. There is no satisfactory form of treatment.[274]

Pericarditis.—In a study of the records of 96 cases of acute pericarditis, the causes were as follows: rheumatic fever, 41%; pyogenic infection, 20%; uremia, 11%; unknown infection (benign, nonspecific, viral), 10%; tuberculosis, 7%; neoplasm, 2%, and unknown, 5%.[275] Gormsen reported seven cases of acute benign pericarditis. Antibiotics are ineffective in therapy.[276] Mononucleosis as a possible cause is mentioned elsewhere in this review.†

Cholecystitis.—According to Cole, the belief is growing that cholecystitis begins primarily not as an infection but as a chemical lesion followed by secondary bacterial invasion.[277] Liver tissue obtained at biopsy rarely contains bacteria. Of 85 specimens obtained from normal persons and from patients with hepatitis or cirrhosis, only 2 contained bacteria.[278]

Colitis.—The cause of pseudomembranous colitis is unknown. Studies reveal that the condition has not become commoner since the introduction of broad-spectrum antibiotic therapy. It often follows shock and may be associated with ischemia of the intestinal wall.[279]

Periodic Peritonitis.—Reference previously was made in these reviews to curious disorders of unknown cause which recur regularly or irregularly at short intervals for many years without affecting the general health of the victims. When the episodes are accompanied by fever and leucocytosis, some infection may be suspected and unnecessary medical or surgical treatment may be applied. I have collected and studied nearly 80 cases of periodic peritonitis among Armenians and Arabs in the Near East. In one family there were 20 victims in five generations. In the United States the disorder is seen more often in Jews. The episodes simulate acute appendicitis or other acute abdominal or thoracic disease, and many patients have had appendectomy or cholecystectomy performed, but the episodes continue unabated. Examination of appendixes reveals sterile inflammation with edema and invasion of plasma cells and polymorphonuclear cells in the serosa, extending toward, but not involving, the mucosa.[280]

"New Diseases."—A possible new entity was observed as "phlebodynia." The disease, apparently in epidemic form, affected 22 nurses, with pain and tenderness along the course of superficial venous tracts of the extremities. Studies failed to reveal a cause.[281]

Because of changes in methods of harvesting and of mild winters, a disease called grain-itch has reappeared in epidemic form in the past two years. It was observed several decades ago and was found to be caused by a mite, Pyemotes ventricosus, which lives on the larvas of grain-destroying insects.[282] Another curious itching eruption of unknown cause occurs in persons who dig in sand for clams. The lesions resemble those of schistosome dermatitis (swimmers itch) contracted in fresh water. Perhaps other cercarias which live in salt water may be the cause.[283]

Epidemiology.—In a study of the effect of famine on the incidence of infectious disease in concentration camps, Danish observers found no absolute relationship

† References 141-143.

between the degree of inanition, weight loss, and the prevalence of infections of the respiratory tract. Exposure to infection, as in normal persons, was most important. Pneumonia and pleurisy affected mainly those who lost the most weight. Infections of the skin were due mostly to lack of bathing facilities, trauma, and poor care. Diarrhea was prevalent but was not regarded as caused by infection. Pathogenic enteric bacteria rarely were encountered. Infectious hepatitis and typhus were seen but were not necessarily related to inanition. Large scale epidemics of any kind did not occur. It was concluded that the increased incidence only of pneumonia, dermal infections, and tuberculosis bore a relationship to nutritional deficiency.[284]

Kempe points out the importance of families as reservoirs of infection. Infection by various bacteria if perpetuated in a group and spread from person to person may cause a variety of diseases according to its localization. Infection can be controlled only by eliminating the causative bacterium from all members at once. Several examples in family groups are described, caused by staphylococci, hemolytic streptococci, and pneumococci. In one family, pneumococci of Types III and V caused fever, otitis, sinusitis, pharyngitis, bacteremia, vaginitis, and peritonitis in different members.[285]

Evidently little progress has been made in the control of cross infection in hospitals since the recommendations of Chapin appeared 35 years ago. Ultraviolet irradiation of air, aerosols, and oiling of floors and of bed-linen have little effect on the spread of infection. Chemoprophylaxis and antibiotic prophylaxis are not recommended. Patients with severe skin lesions and nasal discharges are particularly dangerous as spreaders of infection.[286]

Paper money handled in regions where hygienic habits are primitive was suspected as a carrier of pathogenic bacteria, but tests revealed only bacteria of the coli-aerogenes group. No amebic cysts were found. Coins seldom gave positive results.[287]

Abrasions acquired in swimming pools occasionally result in superficial granulomas of unknown cause. Nine cases are described. Tuberculosis, mycosis, and silica granuloma were suspected as causes. Tubercle bacilli were not found.[288]

In an attempt to minimize the number of injections of vaccines for prophylaxis against certain infectious diseases, combinations of antigens are being used with increasing frequency. The advisability of such procedure has been questioned editorially. In reported instances, for example, by combining scarlet fever and diphtheria immunization, immunity evoked to the latter was unsatisfactory. Similar interference was noted after diphtheria-tetanus-typhoid prophylaxis. Apparently a satisfactory response to one antigen may suppress a response to the other. The matter needs further study to permit proper combinations of antigens.[289]

Cortisone.—Cortisone is said to inhibit the rapid production of antibody, especially that associated with an anamnestic or secondary response.[290] No mention was made of the nonspecific enhancing effect of fibrinogen either in specific precipitation or in agglutination reactions. If adrenal hormones reduce the amount of fibrinogen, this factor may play a role and confuse the issue.

When cortisone is given with minimal curative doses of antibiotic agents, it appears to impair the therapeutic activity of the latter. With larger doses of antibiotics, the inhibiting effect of cortisone is less harmful, because the defense mechanism of the host is then not so greatly needed.[291]

Disappointingly, treatment with cortisone or with urethan did not lower the resistance of monkeys during attempts to transmit viral hepatitis or infectious mononucleosis experimentally. Inoculation of material from patients failed to cause either disease.[292]

Irradiation.—It is known that x-irradiation adversely affects phagocytosis and the normal barriers against bacterial infections. Recent studies add further knowledge about depression of the humoral bactericidal activity in irradiated rabbits. The effect is greatest on the fifth day and disappears 20 days after irradiation.[293] In other studies, granulopenia at the time of inoculation was not responsible alone for increased susceptibility. Great increase in susceptibility to infection began as early as 8 hours after irradiation and lasted 60 days after exposure to 450 r.[294]

In experiments in mice, resistance to Salmonella typhimurium was dependent on a complex interaction of factors involving nonspecific resistance. Mice bred to a strain with a high leucocyte count, a factor once believed to be effective in increased resistance, were no more resistant to infection than other mice.[295]

Germ-Free Animals.—Rats can be reared and kept completely free from microorganisms by a complex technical arrangement in sealed chambers. The longest period they were observed was 18 months. "Sterile" animals breed normally. Their livers are smaller, and they have less lymphoid tissue. No factors related to bacteria or their effects were noted in regard to the formation of vitamins needed for growth. After injection of vaccines, antibodies appear as they do in ordinary animals.[296]

Biologic Interference.—If two related or unrelated viruses are inoculated at the same time, one may prevent the invasion and activity of the other. Interference was demonstrated with one kind of Coxsackie virus but not with another when they were inoculated with poliomyelitis virus.[297] In another experiment guinea pigs infected with Rickettsia rickettsii of low virulence were protected against infection with a highly virulent strain inoculated simultaneously. Similar interference was afforded by inoculation with the rickettsia of Q fever, scrub typhus, and murine typhus.[298] Interference also occurred among strains of related poliomyelitis viruses.[299] There are, however, numerous examples of simultaneous infection. One of the most striking was shown by Japanese investigators. Rickettsia of tsutsugamushi disease and of typhus were both demonstrated microscopically in the cells lining the peritoneal cavity of inoculated mice.[300] In another study there was no interference when the viruses of distemper and canine hepatitis were inoculated in dogs. Both viruses appeared in the blood; inclusion bodies of both viruses were found, and later there was immunity against both viruses.[301]

Bacterial Genetics.—Further studies on the Pneumococcus show how much more complicated variation is than the apparently simple M-S-R variation, as proposed 30 years ago. Recombination of independently heritable characteristics in sexually reproducing forms yielded 18 out of 20 predicted variants.[302] Designation of these variants seems to be as complicated as the alphabetic and numeric nomenclature among Salmonella and Shigella.

Lederberg and Tatum summarize evidence to show that bacteria, like higher organisms, have analogous genetic systems, including nuclei, genes, and even true sexual mechanisms, involving cell-to-cell contact for the recombination of unit characters.[303] Hirst and Gotlieb amplified the observations of Hershey concerning

genetic transmission of characteristics in viruses. By inoculating two strains of influenza virus in eggs they obtained a new stable strain, which contained antigens derived from both "parent" strains.[304]

Under the title of an annotation "mating among viruses," experiments are referred to in which different bacteriophages or different viruses when inoculated together may give rise to "litters" with mixed characteristics, suggesting that hereditary influences were at play.[305] The problem was discussed editorially.[306]

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Case Reports

EXTRARENAL HYPERNEPHROMA

Report of a Case

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CASES of extrarenal hypernephroma are still rare. Reporting of all such cases seems warranted. Ewing, in the first edition of his book, described a group of kidney tumors in general terms as adrenal rest tumors.[1]

Clinically, true kidney hypernephroma is notable for its slow growth and insidious evolution; consequently, the surgical specimens are relatively large.

Geshichter and Widenhorn, in 1934, reported a review of 900 cases, in which they stated that 90% of granular cell tumors occur under the age of 60 years, whereas less than 65% of the clear cell type had a similar age distribution. The clear cell types were slower-growing tumors.[2]

Barney,[3] in 1939, described rare extrarenal hypernephromata as tumors arising from epithelium and adrenal rests. He was able to find 14 cases of so-called hypernephromata of extrarenal origin. He describes a case in which the patient had a prolonged convalescence after a suprapubic prostatectomy, necessitating further study, which upon retrograde pyelography revealed a huge partially calcified tumor occupying the lower pole of the right kidney. Operation revealed a retroperitoneal tumor mass which extended well up under the costal margin and apparently was continuous with the kidney. There was a line of cleavage, and it could be separated from the kidney. The patient recovered. A microscopic section of the tumor revealed various-sized polyhedral cells with sharp borders, small pyknotic nuclei, and very clear cytoplasm. The patient survived for four years and died of coronary occlusion, with no evidence of metastases.

Chiari [4] was the first to call attention to these cases. He reported one case occurring in a man of 44 years in which the tumor, the size of a man's head, was found in the right abdomen between the kidney and the brim of the pelvis. It was retroperitoneal and lay upon the quadratus lumborum and psoas muscles, densely adherent to its surroundings. This patient had a recurrence eight months after operation, at which time a careful histological study showed it to be an accessory adrenal or adrenal tissue growing atypically. From a study of this case, Chiari considered that the tumor arose from accessory adrenal tissue.

From 1901-1929 no instance of extrarenal hypernephroma seems to have been described.

Kapitanoff reported a case associated with the upper pole of the kidney.

In 1936, Melchior [5] described a case wherein the enormous tumor lay under the diaphragm, and by its pressure produced very appreciable atrophy of the right lobe of the liver and of the right kidney.

Being extrarenal, the neoplasm is unlikely to give rise to symptoms referable to the kidney, especially hematuria.

REPORT OF A CASE

A 56-year-old white woman first was seen on June 18, 1951, because of constipation and pain in the left lower abdomen. She also complained of a dry cough and had been to several other physicians, but no cause for the cough had been found. For the past five months she had had an increased sedimentation rate. One interesting, and later proved significant, complaint was a feeling of discomfort following a bowel movement. There was no history of weight loss and no bloody or tarry stool. Her past history was essentially negative, as was her surgical history.

The family history revealed that one of her sisters died of infection with acid-fast organisms. She had had three children and no miscarriages or vaginal bleeding.

Physical examination at this time revealed a 56-year-old white woman not acutely ill. The blood pressure was 130/80; pulse rate, 120; weight, 150 lb. (67.5 kg.), and temperature, 98.6 F. Physical findings, including a pelvic and rectal examination were essentially normal, except for 1+ pitting edema of the lower legs and tachycardia (heart rate 120 per minute). An ECG revealed normal sinus rhythm and a left axis deviation. Proctosigmoidoscopy was entirely normal. A complete blood cell count did not reveal anything of significance. The erythrocyte sedimentation rate was 26 mm. in one hour (Wintrobe). X-ray of the chest revealed no significant pathology. The clinical impression at this time, in view of the cough, tachycardia, and peripheral edema, was of early congestive failure. She was treated accordingly.

The patient was not seen again until Jan. 12, 1952. In the six-month interval she was treated by her family physician. At this time, her complaints were pains in the upper abdomen, dizziness, nausea, and constipation. Examination at this time revealed her blood pressure to be 120/80; her weight was 157½ lb. (70.9 kg.). Chest examination revealed no significant findings. In the abdomen there was a mass in the left upper quadrant which seemed to move with respiration, had a firm edge, and appeared to be the spleen. It was difficult to rule out a retroperitoneal mass which could have displaced the intestinal viscera, giving an impression of spleen. The mass appeared to be 3 to 4 fingerbreadths below the left costal margin. A complete blood cell count revealed no significant findings. Further examinations were performed at Mt. Sinai Hospital Diagnostic Clinic.

While there, the patient gave the following history:

Two months previously she began to feel weak and complained of pain in the left upper abdomen. The pain was persistent and had no relation to intake of food. However, the pain subsided somewhat after a bowel movement. She also complained of a dry nonproductive cough of about 11 months' duration. There was no progressive loss of weight and no history of urinary disturbance. Her appetite had always been good, but she could take only a small amount of food at a time because of a sensation of fullness. She had normal menses up until seven years ago, at which time they ceased without any climacteric symptoms.

Physical findings were essentially the same as mentioned previously. The liver was felt at the costal margin. Near the left costal margin an edge could be felt, which most probably belonged to the spleen. At the lateral border of this edge a mass could be palpated, the surface of which seemed to be uneven. This mass was slightly tender. It was difficult to determine whether this mass was part of the spleen or was attached to the kidney or was a separate mass in the retroperitoneal space.

Fluoroscopy did not reveal any significant findings.

Examination of the urine showed no abnormalities.

Studies of the blood showed 13.8 gm. of hemoglobin and 6,600 white blood cells, with 51% segmented cells, 6% nonsegmented cells, 36% lymphocytes, 3% monocytes, and 4% eosinophiles. The sedimentation rate was 36 mm. in one hour (Westergren). Wassermann and Kahn tests were negative. Blood glucose was 85 mg.; cholesterol, 220 mg., total protein, 7.61 gm.; albumin, 4.06 gm.; globulin, 3.55 gm., and bilirubin, 0.3 mg. per 100 cc.

A test for occult blood in the stool was negative.

An electrocardiogram revealed no abnormality.

The report on the roentgenograms follows:

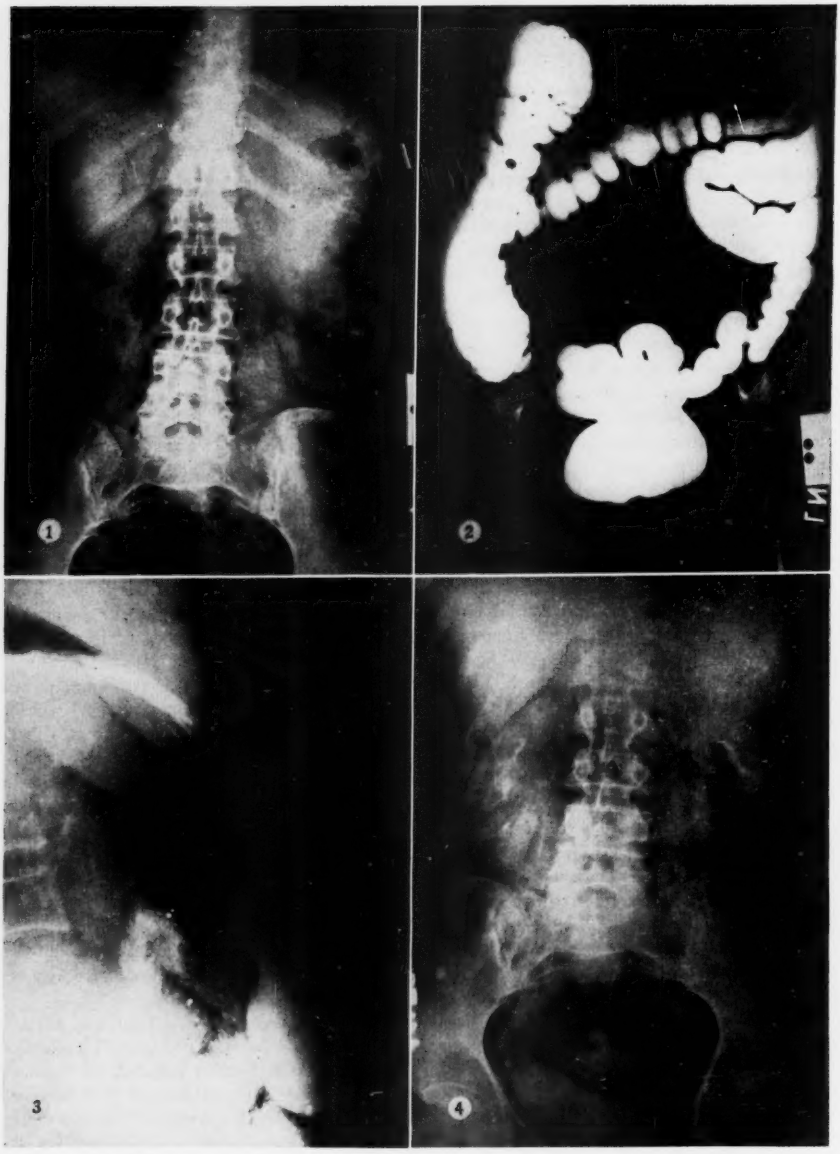

Fig. 1.—Preliminary examination of the abdomen showed multiple amorphous calcifications in the left upper quadrant. There is a suggestion of a mass in this area, with a round curvilinear border. The upper border of this mass is not made out with certainty. The lower border extends well over the left kidney.

Fig. 2.—There is extrinsic pressure on the bowel in the region of the splenic flexure.

Fig. 3.—Film showing the vertical portion of the stomach displaced to the right.

Fig. 4.—Intravenous pyelogram, revealing prompt excretion bilaterally. There is incomplete filling of the left upper urinary tract. The upper and lower thirds of the right ureter are normal. On the left side, the middle infundibulum appears to be displaced downward in a gentle arc. There appears to be a kinking of the superior infundibulum. The visualized portion of the left ureter appears normal. The bladder shows a concavity on the superior aspect, presumably due to extension by the uterus.

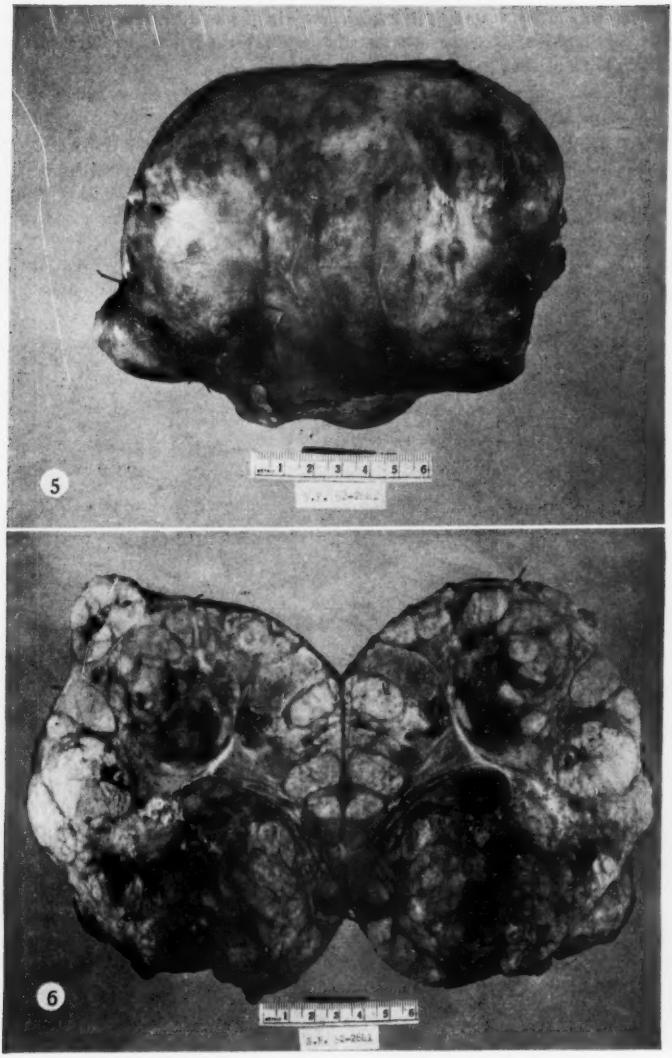

Fig. 5.—Gross specimen consisting of an irregularly shaped mass measuring 18 by 12.5 by 7 cm. The external surface is pink-grey and is covered by fibrous tissue tags.

Fig. 6.—Cut section revealing a well-encapsulated mass which is tan-yellow, trabeculated, and separated by firm fibrous bands and which reveals areas of softening alternating with areas of marked firmness.

The chest film shows the left leaf of the diaphragm to be high. There is calcification in the wall of the aorta. There is marked kyphoscoliosis of the dorsal spine, with considerable osteoporosis of all the visualized bones.

The dorsal spine shows no abnormalities aside from the presence of hypertrophic osteoarthritis. Incidentally, there is noted the fact that the left 12th rib is considerably shorter than its counterpart on the right side.

Preliminary examination of the abdomen shows multiple amorphous calicifications in the left upper quadrant (Fig. 1).

There is a suggestion of a mass in this region, with a round curvilinear border. The upper border of this mass is not made out with certainty. The lower round and broad border of this mass does not conform to the edge of the spleen as it is usually seen. Both kidneys are normal in size and shape and position. Both psoas shadows are distinct. There is no evidence of opaque biliary or renal calculi.

Barium enema study shows no intrinsic abnormality of the large bowel. There is extrinsic pressure on the bowel in the region of splenic flexure (Fig. 2).

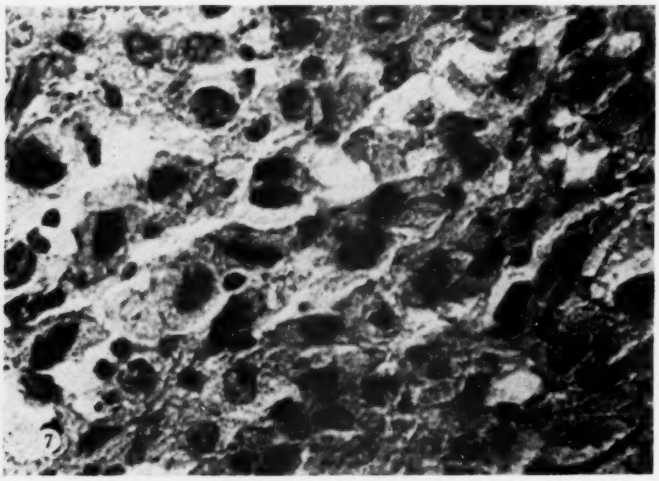

Fig. 7.—Microscopic section of the tumor mass revealing the large irregularly shaped polygonal cells of varying size and shape. The cell outlines are indistinct. The nuclei are relatively small. The cytoplasm is granular and is pink in some areas and clear in others. Many cells are giant cells, and some contain more than one nucleus.

Barium meal study shows no evidence of intrinsic abnormality of the esophagus or stomach. A large retrogastric mass is seen, which contains the previously described calcification. This increases the retrogastric space and causes, in addition, the vertical portion of the stomach to be displaced toward the right (Fig. 3). The duodenal bulb and loop are normal. The small bowel in the left upper quadrant is displaced downward by the previously described mass.

Intravenous pyelogram reveals prompt excretion bilaterally. There is incomplete filling of the left upper urinary tract, and the visualized portions show no evidence of abnormality or dilatation. The upper thirds of the right ureter are visualized and appear normal. On the left side, the middle infundibulum appears to be displaced downward in a gentle arc. There also appears to be kinking of the superior infundibulum. The visualized portion of the left ureter appears normal. The bladder shows a concavity on the superior aspect, presumably due to extension by the uterus (Fig. 4).

The patient returned for examination on March 30, 1952, at which time she was advised of the findings and was told that an exploratory operation would be necessary to determine the true

nature of this mass in the abdomen. Prior to operation a bone marrow study revealed a normal marrow. This finding more strongly favored the diagnosis of a retroperitoneal tumor and not that of a splenic one.

The patient was admitted to the Jewish Hospital, Brooklyn, in May 1952, and was operated on by one of us (G. S.).

Findings at Operation.—There was a huge mass, lobulated and rubbery in consistency, occupying the retroperitoneal space immediately below the diaphragm in the left upper quadrant. This mass measured about 22 cm. in its vertical diameter and about 16.0 cm. in its transverse diameter. It was lying across and compressing the upper pole of the left kidney and had displaced the spleen upward and anteriorly. The tumor was lying directly on the aorta. It was moderately adherent to the under surface of the diaphragm but was covered by a definite capsule. The origin of the mass was not from the spleen or from the pancreas, and it was impossible to determine whether it arose from the left adrenal gland. The left adrenal could not be found. The other organs in the abdominal cavity were normal.

Postoperative Course.—The patient had a very uneventful postoperative course and was discharged from the hospital on the 14th day.

At present, two years after surgery, the patient is enjoying good health, with no evidence of any metastases.

Description of the Pathological Specimen.—Gross Appearance: The specimen consists of an irregularly shaped mass measuring 18 by 12.5 by 7 cm. The external surface is a pink-grey and is covered by fibrous tissue tags. The cut section reveals a well-encapsulated mass which is tan-yellow, trabeculated, and separated by firm fibrous bands and which reveals areas of softening alternating with areas of marked firmness (Figs. 5 and 6). Several areas of necrosis are noted together with areas of hemorrhage.

Microscopic Appearance: The preparation shows a somewhat variegated picture. The tumor consists of sheets and nests of large irregularly polygonal cells of varying size and shape. The cell outlines are distinct. The nuclei are relatively small. The cytoplasm is granular and is pink in some areas and clear in others. There are foci of necrosis, and scattered throughout are some osseous tissue and calcific deposits. Many cells are giant cells, and some contain more than one nucleus. There are foci of extravasated blood. The tumor resembles one arising from the kidney or adrenal gland (Fig. 7).

COMMENT

A case of extrarenal hypernephroma is presented which appears to fit in with the case described by Melchior.[5] It seems to represent a "true" extrarenal hypernephroma arising from an adrenal cell rest. The cells of the tumor were mixed, granular and clear cells being present, and thus is in accordance with the microscopic findings of nephrogenic tumors or tumors arising from adrenal rests, whether extrarenal or intrarenal.

Making a definite diagnosis of such a tumor preoperatively is practically impossible. However, certain procedures should be carried out to determine whether one is dealing with a retroperitoneal tumor. These consist of a flat film of the abdomen, complete gastrointestinal series, and an intravenous pyelogram. The location of the mass and the finding of multiple calcific areas should make one suspect that an extrarenal tumor exists.

It is worth noting that there were no endocrine changes in our patient. Also noted is the relative slowness of growth and tendency to encapsulation of the tumor.

Marchand * conceived the genesis of secondary adrenals as being prematurely squeezed-off groups of cells of the adrenal gland, these being drawn downwards along the spermatic vein with the descent of the testicle or ovary. Since he was never able to demonstrate adrenal rests in the adult, he took the view that they

* Cited by Ewing.[7]

gradually disappeared during childhood. Chiari,[4] on the other hand, stated that these rests may occur not only in the newborn and young children but also in the adult. According to Ewing,[7] this view was later substantiated by others, who found that the adult peritoneal epithelium is capable of developing foci of adrenal tissue. Such rests are infrequent in the kidney. They are not infrequently found on the under surface of the liver, on the epididymis, on the broad ligaments and ovarian veins, and occasionally in the testes. They may also be found in association with the suprarenal veins, solar plexus, uterus and ovary, pancreas, and transverse colon.

It is interesting to mention and at least speculate on the question of why our patient did not develop metastases. As a rule, the capsule surrounding the tumor is smooth and does not present evidence of rupture. Metastases are primarily blood-borne, lymphatic spread occurring late, at a time when, as a result of necrosis, the tumor has ruptured and has subsequently invaded the surrounding structures.

Generally, these tumors have a dense fibrous capsule which delimits the tumor. Often the capsule confines the growth so well that when the fresh surgically removed specimen is cut in two the tumor, released from its confining capsule, bulges outward. Clear cell carcinoma is not actively invasive but is rather expansile. It advances on a solid front and does not send out finger-like strands of cells into normal tissues.[8]

Our case has been under observation for a period of two years after surgery, with no evidence of metastases and no subjective complaints from the patient. Her general physical examination reveals no significant findings. Her blood picture has remained normal.

SUMMARY AND CONCLUSIONS

A brief review of the literature dealing with extrarenal hypernephromas is summarized.

A case of extrarenal cell carcinoma with clinical, roentgenological, operative, and pathological findings is cited.

A brief discussion of the case, coordinating operative and pathological findings, is given.

The subject of metastases in this kind of tumor is stressed, especially from a pathological viewpoint.

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THROMBOCYTOPENIC PURPURA ASSOCIATED WITH CAT-SCRATCH DISEASE

Response of Cat-Scratch Disease to Steroid Hormones

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AND
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IT IS THE purpose of this paper to report the occurrence of thrombocytopenic purpura during typical cat-scratch disease and the probable relationship of the two conditions. This association has not previously been noted in the literature. It is the further purpose of this paper to note the salutory effects of corticotropin (ACTH) and cortisone on the lymphadenopathy of cat-scratch disease, another fact not previous reported.

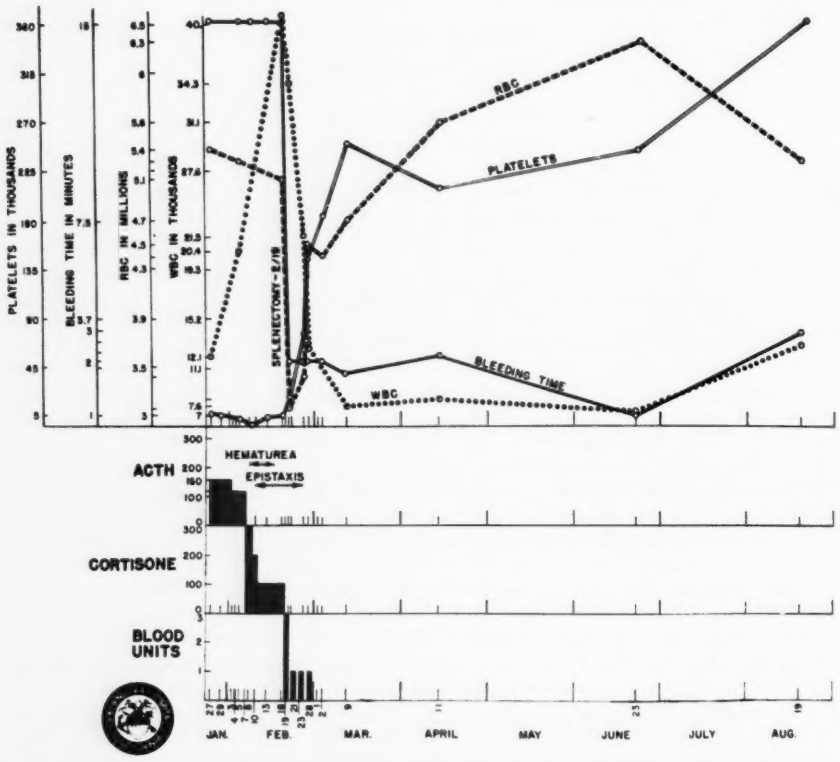
REPORT OF A CASE

A 26-year-old grade school teacher was admitted to the hospital on Jan. 27, 1953. Five weeks before admission he had been scratched on the tip of the fourth finger of his right hand by his cat. After several days the scratch began to swell, and a few days later the patient noted painful swelling of a right axillary lymph node, followed in one week by painful swelling of a right epitrochlear lymph node. During this period the patient felt fatigued, ached generally, and had mild headache. He continued to teach school. After several weeks pain in the lymph nodes diminished somewhat, but they remained as large as ever. About Jan. 17, 1953, he had a routine dental examination and was told that he had impacted lower third molars. He felt that these might be contributing to his lymph node swelling, and so he had the teeth extracted. The extraction was done under thiopental (Pentothal) sodium, without incident. An injection of penicillin procaine was given immediately afterward. He subsequently took acetylsalicylic acid, phenacetin, and caffine (Empirin) Compound with codeine on several occasions and also took both ephedrine and epinephrine (Adrenalin) for mild asthma, to which he had been subject for several years. During the entire course of his illness he had taken no other medications and had come in contact with no chemicals. The lower right third molar area oozed from the time of extraction. The area of extraction on the left did not ooze at all. On Jan. 23, 1953, the patient noted several small red spots on his skin which bled if scratched and also noted that his gums were bleeding and that he passed a small amount of bright red blood in his stool. A platelet count was found to be below 5,400, and the patient was therefore hospitalized for investigation. The cat had continued to remain in the patient's household, and during January it had scratched the patient's wife. Neither the cat nor the patient's wife had shown signs of illness. Past history indicated that the patient had had measles, mumps, chickenpox, whooping cough, and scarlet fever in childhood. Neither the patient nor any member of his family had ever shown any hemorrhagic manifestations.

Physical examination revealed a well-developed well-nourished young man in no distress. He was mentally clear and cooperative. The temperature was 98.6 F.; pulse rate, 72, and blood pressure, 120/70. There were scattered groups of tiny petechial lesions on the arms, legs, and

From the Veterans Administration Hospital.

trunk. A small razor cut on the right cheek incurred the day of admission was still oozing and covered with crusted blood. A right epitrochlear lymph node was about 5 cm. in diameter and tender. The overlying skin was violaceous. There was a right axillary lymph node of similar size and tenderness. There was no other significant adenopathy. Three small subconjunctival hemorrhages of the palpebral conjunctiva on the left were noted. The eye grounds were normal. A few petechiae were present on the external ears. The drums appeared normal. Both lower third molars had recently been extracted. A small amount of packing was present on the right. There was no obvious bleeding from either socket. The gums appeared normal, although there was a small area of ecchymosis adjacent to the left third molar extraction. The



Summary of a case of thrombocytopenic purpura associated with cat-scratch disease.

chest was entirely clear. Cardiovascular examination showed no abnormality. A small scar from the previous cat-scratch was noted on the tip of the right fourth finger. The liver and spleen were not palpable, either on admission or at any time subsequently.

Laboratory Findings.—See the Chart for serial changes in the platelet count, bleeding time, red cell count, and white cell count. Coagulation times were repeatedly normal; clot retraction was incomplete (after 24 hours) prior to splenectomy, on Feb. 19, and entirely normal thereafter. The roentgenogram of the heart and lungs was within normal limits.

Course and Treatment.—A diagnosis of cat-scratch disease and thrombocytopenic purpura was made. Bone marrow aspiration the day of admission showed marked megakaryocytic hyperplasia, with some arrest of maturation and absence of platelet budding. The myeloid and eryth-

roid elements were normal. The patient was then placed on 40 mg. of corticotropin at six-hour intervals after a blood survey and the bone marrow aspiration. Lymph node biopsy was not performed because of the patient's bleeding tendency. By Feb. 2, 1953, no change had occurred in the patient's blood picture, but he had not developed new petechiae and the razor cut on his face, present on admission, was no longer oozing. It was noted that the enlarged epitrochlear and axillary lymph nodes had become half their former size and were no longer tender or violaceous. By Feb. 8 the lymph nodes were reduced to small nubbins, less than 1 cm. in maximum diameter. On Feb. 8 gross hematuria began. Corticotropin was discontinued, and the patient was given 300 mg. of cortisone in divided doses. Gross hematuria gradually diminished over the next three days. On Feb. 10, 1953, epistaxis occurred for the first time. From then on, despite frequent packing and cauterization the patient continued to bleed from either the right or the left external naris. By Feb. 18, 1953, it was felt that corticotropin and cortisone had been given ample trial, without success so far as the patient's bleeding tendency or platelet count were concerned, and that splenectomy was warranted. By this time no trace of right epitrochlear and axillary adenopathy remained. On Feb. 19 a splenectomy was performed. Bleeding was not excessive, but several transfusions were required to raise the patient's hemoglobin and red cell count to satisfactory levels (see the Chart).

The spleen weighed 225 gm. The capsule was not thickened. Malpighian bodies were tiny but distinct. Microscopically, Malpighian bodies were not numerous, but the lymphatic sheaths were prominent. The reticuloendothelial cells of the red pulp were prominent and had abundant foamy cytoplasm containing cellular and nuclear fragments. In the germinal centers phagocytosis of nuclear fragments, possibly representing platelet phogocytosis, was prominent. There was no evidence of malignant change or specific inflammation. Microscopic diagnosis was "spleen compatible with thrombocytopenic purpura."

The patient's postoperative course was essentially uneventful. The platelet count mounted steadily, reaching 245,000 on March 13, the day of discharge. The red cell count, with the aid of transfusions, returned to normal limits. For two days following surgery occasional mild epistaxis occurred, apparently from an extensively ulcerated area, which was probably attributable to frequent cauterizations during the patient's preoperative period. Cortisone therapy was terminated the day of surgery and was not resumed thereafter. On March 2, 1953, 0.1 cc. of cat-scratch antigen, obtained through the courtesy of Dr. Worth B. Daniels, of Washington, D. C., was injected intracutaneously. In 48 hours an area of induration 7 mm. in diameter was present, surrounded by a 15 mm. faint red flare. The induration area persisted up to the time of discharge. The flare disappeared after 96 hours. Seventy-two hours after injection of the cat-scratch antigen the patient developed a few small groups of petechiae, confined to the dependent portions of the lower extremities. No further showers occurred thereafter. At that time the patient's platelet count was over 200,000, the bleeding time was two minutes, and the Rumpel-Leede test was negative. A bone marrow aspiration performed March 5 showed megakaryocytes in greater numbers than normal, but most of these were of mature type and were budding platelets normally. Again the myeloid and erythroid elements were normal. The patient was discharged with maximum hospital benefit, and when he was seen one month and six months later he felt entirely well, had normal hematologic findings, and had had no recurrence of petechiae.

COMMENT

Thrombocytopenic purpura has previously been reported to have occurred with a wide variety of infections of both bacterial and virus origin, including rubella, diphtheria, scarlet fever, varicella, roseola, tuberculosis, and infectious mononucleosis.[1] The interval between the onset of the infection and the appearance of purpura has varied widely, occurring in the acute stages of an infection or well in the period of convalescence.[2] Our patient was in the sixth week of his cat-scratch disease when his purpura first became manifest. His enlarged lymph nodes were still painful and tender and appeared violaceous, suggesting continuing activity. He received Empirin compound with codeine, thiopental sodium, and penicillin procaine after

dental extractions prior to the development of purpura. None of these drugs has been incriminated as a cause of thrombocytopenic purpura, although other barbiturates have, and sodium salicylate was suspected in one fatal case.[3] It was our wish to test the patient's sensitivity to these drugs after recovery, but the splenectomy would perhaps have altered the patient's hematologic response enough to render a provocative test indecisive, and, in addition, he did not wish to run any possible risk of recurrence of his bleeding, especially after splenectomy.

It is stated that recovery from purpura due to infection is usually rapid and complete and that if recovery does not occur or if there is a residual hemorrhagic tendency it is probable that the patient is suffering from coincidental thronic purpura and that the infection stimulated an exacerbation of the symptoms.[2] Actually, we interrupted the natural course of our patient's thrombocytopenic purpura during the fourth or fifth week, which is not a sufficiently long period of time to rule out purpura due to infection. It was our feeling at that time that the continued severe thrombocytopenia, prolonged bleeding time, and frank hemorrhage in the absence of any response to either corticotropin or cortisone was sufficient indication for surgery, though Hirsch and Dameshek [4] suggest an observation period of four months, during which period recovery of thrombocytopenia due to infections or drugs may be expected. The fear of damaging or fatal cerebral hemorrhage exists whenever a patient is bleeding elsewhere, and neither we nor our patient cared to accept that calculated risk after failure of response to steroid hormones. Decision in favor of splenectomy might have obscured the etiology of the patient's thrombocytopenia, but so far it has been fully successful therapeutically, the patient having shown a normal blood cell count, a platelet count of 363,000, and a bleeding time of 2 minutes and 50 seconds, six months after splenectomy.

Even though corticotropin was without effect on the patient's blood picture, its use led to the rapid disappearance of the patient's two large tender lymph nodes during 10 days of therapy. It would not have been anticipated that lymphadenopathy of such long duration would have resolved so rapidly spontaneously. Daniels and MacMurray * felt that chloramphenicol (Chloromycetin) given early shortened the course of the disease and led to rapid clearing of lymphadenopathy and cited Debré as having the same opinion with regard to chlortetracycline (Aureomycin), but in their successful cases the patients were treated rather earlier than this patient.

Whether the short episode of purpura 72 hours after administration of cat-scratch antigen, at the peak of the reaction, was coincidence or was an allergic response is a matter for speculation.

SUMMARY AND CONCLUSIONS

A case of thrombocytopenic purpura associated with and possibly secondary to cat-scratch disease is reported.

There was failure of response of the thrombocytopenia and bleeding tendency to corticotropin (ACTH) and cortisone, but there was apparent cure following splenectomy. The patient remains normal six months after splenectomy.

Unusually rapid disappearance of the lymphadenopathy of cat-scratch disease occurred with corticotropin therapy.

* References 5 and 6.

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ACUTE ADRENAL INSUFFICIENCY

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CLINICALLY, it has been established that the prolonged use of cortisone results in a temporary depression of the adrenal secretions. It is this depressive effect on adrenal function that makes it possible to control carcinoma of the prostate gland after orchectomy and the estrogens have lost their therapeutic effect. Sudden withdrawal of cortisone may result in an acute adrenal insufficiency. Hydrocortisone is a drug equivalent to cortisone in its physiological effects on the patient. We recently treated a patient for acute adrenal crisis when hydrocortisone had been substituted for cortisone. The two drugs have identical physiological effects in the dosage ratio of hydrocortisone 65 mg. to cortisone 100 mg. The literature does not clearly state whether cortisone depresses more adrenal functions than does hydrocortisone. Our experience with this patient suggests there is a difference which may produce serious consequences.

REPORT OF A CASE

A white woman, aged 33, was seen by her family physician (P. C.) in her home at 2:30 p. m. on Dec. 20, 1953. She was found in complete collapse, pulseless and cyanotic, and her blood pressure could not be recorded. The morning prior to her collapse she had vomiting and diarrhea.

Her past history was significant in that her physician had been treating her since 1948 for ulcerative colitis. At that time her liver was enlarged down to the umbilicus. She had a marked secondary anemia, requiring many transfusions, until January, 1951, when she was placed on an oral cortisone regimen, between 50 and 75 mg. per day. Cortisone gave her complete relief of her colitis and anemia. The liver returned to normal size. Whenever the drug was stopped, her symptoms would all return. In addition, she developed large bullous-like wheals on the lower abdomen, palmar surface of the hands, and the inner aspect of the knees. This had been diagnosed as bullous erythema multiforme. With the resumption of cortisone, the colitis and bullous lesions would disappear in from five to seven days.

On Nov. 23, 1953, the cortisone, 50 mg. per day, was stopped and hydrocortisone, 30 mg., was substituted. On Dec. 1 a gradual recurrence of her colitis and bullous lesions was noted, and hydrocortisone, 80 mg. daily, was given. On Dec. 20 severe vomiting and diarrhea developed and the patient collapsed.

The patient was admitted to the City Hospital, of Akron, where examination showed the signs of shock, apprehension, cyanosis, and cold sweating of extremities. The liver was palpable 4 cm. below the right costal margin. Overlying the lower abdominal skin was a large area of black pustular lesions with an erythematous base. Blood pressure and pulse could not be recorded.

Emergency treatment for acute adrenal insufficiency consisted of 100 mg. cortisone and 5 mg. of desoxycorticosterone acetate (DOCA) by hypodermic and 5% dextrose in 1,000 cc. of isotonic sodium chloride solution, to which 2 cc. of arterenol (Nor-epinephrine) had been added. Oxygen by BLB (Boothby, Lovelace, Bulbulian) mask was given. The blood pressure began to rise, and at the completion of the infusion it was 120/80 and the pulse rate was 120. According to the intern's notes, "she made a miraculous recovery." Cortisone, 50 mg., was given every six hours, and the dextrose and saline solution was continued for the next six hours. The RBC count was

4,300,000; hemoglobin value was 84%. Electrolyte studies made the following day showed the serum chloride to be 100 mEq. per liter; the sodium was 130 mEq. per liter, and the potassium was 5.4 mEq. per liter. Within 24 hours the patient was up and about. She was discharged on the fourth hospital day on a maintenance dose of cortisone of 50 mg. per day. The bullous lesions on the abdomen were beginning to heal.

SUMMARY AND CONCLUSIONS

A case report is presented of a woman, aged 33, in whom cortisone, 50 to 75 mg. per day, since 1951 had controlled her ulcerative colitis, secondary anemia, and bullous skin lesions. Substitutions of hydrocortisone failed to control her colitis and skin lesions, and, apparently following an acute stress of vomiting and diarrhea, acute adrenal insufficiency developed.

It is concluded that although the two drugs may have the same physiologic effects their depressing effects on the adrenal secretions may be different.

It is suggested, in changing from cortisone to hydrocortisone therapy, that the cortisone dosage be gradually tapered off at the same time that the hydrocortisone is being started.

Books

Dystrophia musculorum progressiva: Eine genetishe und klinishe Untersuchung der Muskeldystrophien. By Prof. Dr. P. E. Becker. Price, DM 28.50. Pp. 311, with 101 figures. George Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O, 1953.

This book is based on a study of 86 pedigrees of families in Baden, Germany, suffering from progressive muscular dystrophy. More than 6,000 people are included in the geneologies, and of this number 259 had the disease. Clinical studies were made on 159 sufferers. The author finds in his own study and from a review of the literature that there are two basic types of dystrophy —the shoulder-girdle type and the pelvic-girdle type. The latter has two modes of inheritance, and there are therefore three different genetic forms. The shoulder-girdle type is a Mendelian dominant, affecting the sexes equally. The age of onset is from 7 to 25 years, with a peak at 15 to 16. The course is slow. The face may be affected, but the muscles of the neck and of the hand are rarely involved. Pseudohypertrophy occurs in about 25% of cases. Males are more severely involved than are females.

The pelvic-girdle type is inherited in recessive fashion, either sex-linked or autosomal. Both forms of inheritance result in clinical pictures which are somewhat similar to each other but differ from the shoulder-girdle form. The sex-linked form has its onset most often in the first three years of life. The course is rapid, and the disorder ascends to the shoulder girdle but rarely to the face. The neck and small muscles of the hand are involved. Pseudohypertrophy and contractures are common. Death usually occurs in the second decade of life. The recessive autosomal form is similar, but the course is slower and the disease is not as severe as in the sex-linked form.

This subdivision of muscular dystrophy is similar to that proposed by Tyler and Wintrobe, who described a "childhood type," involving axial and pelvic muscles, and a fascioscapulohumeral type. Both these authors and Becker have performed a great service in simplifying a disorder overburdened (from the pedagogic standpoint) with classifications and eponyms. One still has the problem of dealing with many variant and "atypical" forms of dystrophy, especially in sporadic cases in which the hereditary background is not so uniform or clear-cut. Where in these schemes does one put cases of dystrophy involving only ocular muscles, or those that begin distally, or those in families in which only women are affected? The value of this study will be greatest if the inherent over-simplification is appreciated. There is a large bibliography, but an index is lacking.

Endocrinology in Clinical Practice. By Gilbert S. Gordon, M.D., and H. Lisser, M.D. Price, $10.50. Pp. 407. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1953.

The following statement is quoted from the preface. "It is the purpose of this book to present to the practicing physician a digest of material he needs for the diagnosis and treatment of endocrine disorders, and for the use of hormones in diseases which are not primarily endocrine in origin." This aim has been admirably carried out. This book is a ready clinical guide to endocrinology.

The first chapter is devoted to the general principles of making an endocrine diagnosis by history, physical examination, and laboratory data. A section on the general principles of endocrine therapy is included. It is a well-written concise explanation of the approach to an endocrine problem.

Succeeding chapters are The Thyroid Gland; The Parathyroid Glands, Calcium Metabolism, and Metabolic Bone Diseases; The Pituitary Gland; The Adrenals; Carbohydrate Metabolism; Obesity and Leanness; The Gonads; Infertility, and Endocrine Therapy in Neoplastic Diseases. Each chapter covers the field well. Each entity is described; a differential diagnosis is outlined; specific diagnostic methods are described, and specific treatment is outlined. The endocrine preparations recommended for treatment are those most recently available.

The appendix contains descriptions, trade names, and doses of useful endocrine preparations. It is a chapter which the owner of this book will refer to often.

This is a clinical book by clinicians, for clinicians. It is not recommended for endocrinologists. Other physicians will find it a practical guide to endocrinology.

Atomic Medicine. By Charles F. Behrens, M.D. Second edition. Price, $11.00. Pp. 632. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This second edition of the 1949 classic volume on atomic medicine has been brought up to date by thorough revision of the text and expansion of the bibliography. The basic physics, biology, pathology, and clinical effects of ionizing radiations are well discussed. The chapters on the biologic and clinical applications of radioisotopes are excellent. A chapter on dosimetry has been added. While there is a certain amount of repetition, inevitable in a book written by 20 contributors, the general level of presentation of facts and concepts is on a high plane of accuracy, clarity, and interest. This new edition fully deserves a very wide distribution.

Shock and Circulatory Homeostasis. Edited by Harold D. Green, M.D. Price, $3.75. Pp. 275. Josiah Macy Jr. Foundation, 16 W. 46th St., New York 36, 1953.

In this second symposium on shock and circulatory homeostasis, the major space is devoted to an analysis of the metabolic changes in hemorrhagic and traumatic shock (by Frank L. Engel) and the distribution, physiology, and pharmacology of epinephrine and arterenol (Norepinephrine) (by U. S. von Euler).

Apart from the excellence of the formal material in these two categories, there is the usual off-the-cuff and stimulating discussion by the multidisciplined participants in the conference. This report is essentially directed to experts in research on shock and circulatory physiology.

Traitment des Hémorragies. By J. P. Soulier. Price, 1,400 francs. Pp. 217. Ernest Flammarion, 22 rue de Vaugirard, Paris, 1953.

This book is in three parts. The first part discusses hemostatic substances; the second part discusses the treatment of hemorrhagic syndromes; the third part discusses the treatment of local hemorrhage from various organs.

This book is of some value to the medical student or busy practitioner. It summarizes, in sketchy fashion, much of what is known in the above subjects. There is, however, no careful analysis of the many facts presented. There is not a single picture or diagram to break into the recital of facts. The bibliography is not complete; nor is it related to the text, since there is no indication in the text as to which article is being referred to. It is, therefore, not recommended for the hematologist, internist, or practitioner who wants to keep up with the latest developments in medicine and surgery.

The Practical Management of Diabetes. By Edward Tolstoi, M.D. Price, $3.25. Pp. 93. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1953.

This monograph is another member of Thomas' American Lecture Series, edited by Gygorgy, Leiter, and Waife. It is a short, empirical treatise, dealing almost exclusively with details of treatment as used by the author in his liberal approach to diabetes mellitus.

The main theme is to the effect that abnormal glycosuria and hyperglycemia do no harm in diabetes, provided enough insulin is used to prevent symptoms, avoid acidosis, and maintain weight. No proof of this is offered. Refutation of some of the evidence to the contrary is attempted, but it is unconvincing, chiefly because facts are too often ignored and opinions too freely expressed.

The argumentative character of the monograph is offset, to some extent, by short useful descriptions of diabetic acidosis, pregnancy and neonatal care for diabetic mothers and their babies, and arterial and neuropathic complications in the legs and feet.

In some respects it is unfortunate that the use of insulin makes most diabetics feel so well. That fact unquestionably lulls some uncritical physicians and their patients into easy acceptance of expedient methods of treatment, while they remain in complete ignorance of other advantages sacrificed by so doing. Those who do will find an opiate here.

Physiological Methods in Clinical Practice. By William S. Middleton, M.D. Price, $1.00. Pp. 40. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

This paper-backed copy in the American Lecture Series is the Beaumont Lecture delivered by Dr. William Middleton before the Wayne County Medical Society, in Detroit, Mich. It will furnish an hour of stimulating and informative reading to any internist who is really interested in his specialty.

The profound observations of the young Army surgeon, whose only equipment consisted of his five sharp senses and unlimited patience, on Alexis St. Martin are again recounted by a loyal and competent disciple of the physiologic approach to the study of disease. Several bright gems from Beaumont's original writings are quoted: "But we ought not to let ourselves be reduced by the ingenuity of argument or the blandishments of style. Truth, like beauty, when 'unadorned, is adorned the most'; and in pursuing these experiments and inquiries, I believe I have been guided by its light. Facts are more persuasive than arguments, however ingeniously made, and by their eloquence I hope to be able to plead for the support and maintenance of these doctrines."

From Beaumont's experiments the author moves in swift strokes through the fundamental observations of John Young, Spencer, Ewell, Müller, Magendie, Louis, and many others of the nineteenth century. He then shows in a thoroughly delightful manner how physiology has been a great and continuing contributor to modern concepts of disease, resulting in such indispensable procedures as thermometry, recording of blood pressures, electrocardiography, fluoroscopy, cardiac catheterization, biologic chemistry, tests of liver function, determinations of adrenal corticoids, etc.

As might be expected from William Middleton, the fruits of prodigious and skillfully directed hours in the library, class room, and laboratory are compressed in this readable and economical volume.

Electrocardiography. By E. Grey Dimond, M.D. Price, $14.00. Pp. 261, with 272 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1954.

An outgrowth of five years of classroom teaching, this new text of electrocardiography is presented as a series of organized, progressive lectures intended for the medical student. It should prove of particular value to the busy general practitioner who may have been unable to evaluate and assimilate the many recent advances in electrocardiographic application and interpretation. As a method of teaching, it should be of value, also, to the expert.

Dr. Dimond covers the subject thoroughly in 261 well-illustrated pages. He first discusses the merits of the various machines, the correction of technical errors, and the keeping of good records. He then develops the basic concepts and illustrates their application in hypertrophy, block, myocardial disease, arrhythmias, and electrolyte disturbances.

Through liberal use of diagrams and models the concepts of spatial vectorcardiography are introduced and applied with new meaning for the reader. Although experience is acknowledged as still of greater importance in the correct interpretation of electrocardiographic patterns, vector interpretation offers a method by which the electrocardiogram can be better understood.

CORRECTION

In the article "Infiltrative Eosinophilia," by R. S. Días-Rivera, F. Ramos-Morales, and A. A. Cintrón-Rivera, on page 102 of the July, 1954, issue of the ARCHIVES, the names of both authors in Reference 40 (page 119) are misspelled. This Reference should read

40. Fond, I., and Ravenna, P.: Tropical Eosinophilic Asthma, Arch. Int. Med. **82**:422, 1948.

Amebiasis[1] a "Poorly Reported" Disease

Until serious complications arise, amebiasis may pass unrecognized and patients receive only symptomatic treatment.

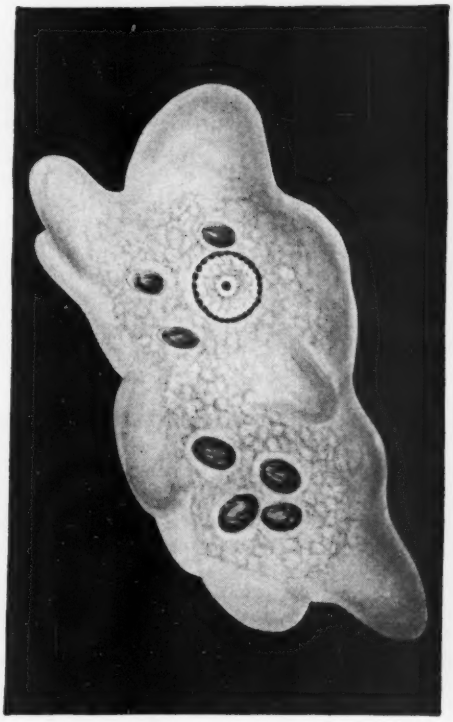
Although amebiasis is a disease with serious morbidity and mortality, statistics on its incidence[1] are incomplete because its manifestations are not commonly recognized and consequently not reported.

"*Vague symptoms[2] referable to the gastrointestinal tract, such as indigestion or indefinite abdominal pains, with or without abnormally formed stools, may result from intestinal amebiasis. Not infrequently in cases in which such symptoms are ascribed to psychoneurosis after extensive x-ray studies have been carried out, complete relief is obtained with antiamebic therapy.*"

To prevent possible development of an incapacitating or even fatal illness and to eliminate a reservoir of infection in the community, diagnosing and treating[3] even seemingly healthy "carriers" and those having mild symptoms of amebiasis is advised.

Early diagnosis[1] is important because infection can be rapidly and completely cleared, with the proper choice of drugs and due consideration for the principles of therapy. For treatment of the bowel phase these authors find Diodoquin "most satisfactory."

For chronic amebic infections, Goodwin[4] finds Diodoquin to be one of the best drugs at present available.



Endamoeba histolytica (*trophozoite*).

Diodoquin, which does not inconvenience the patient or interfere with his normal activities, may be used in the treatment of acute or latent forms of amebiasis. If extraintestinal lesions require the use of emetine, Diodoquin may be administered concurrently. It is a well tolerated and relatively nontoxic orally administered amebacide, containing 63.9 per cent of iodine.

Diodoquin (diiodohydroxyquinoline), available in 10-grain (650 mg.) tablets, reduces the course of treatment to twenty days (three tablets daily). Treatment may be repeated or prolonged without serious toxic effect. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.

---

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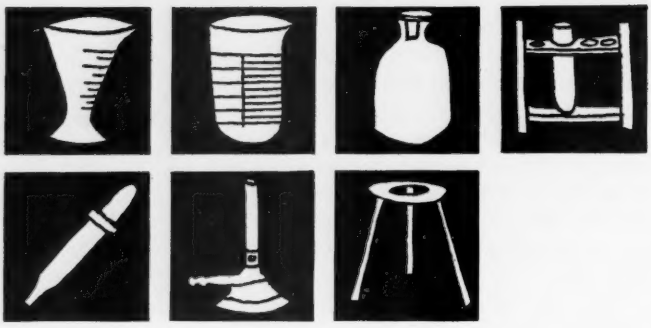

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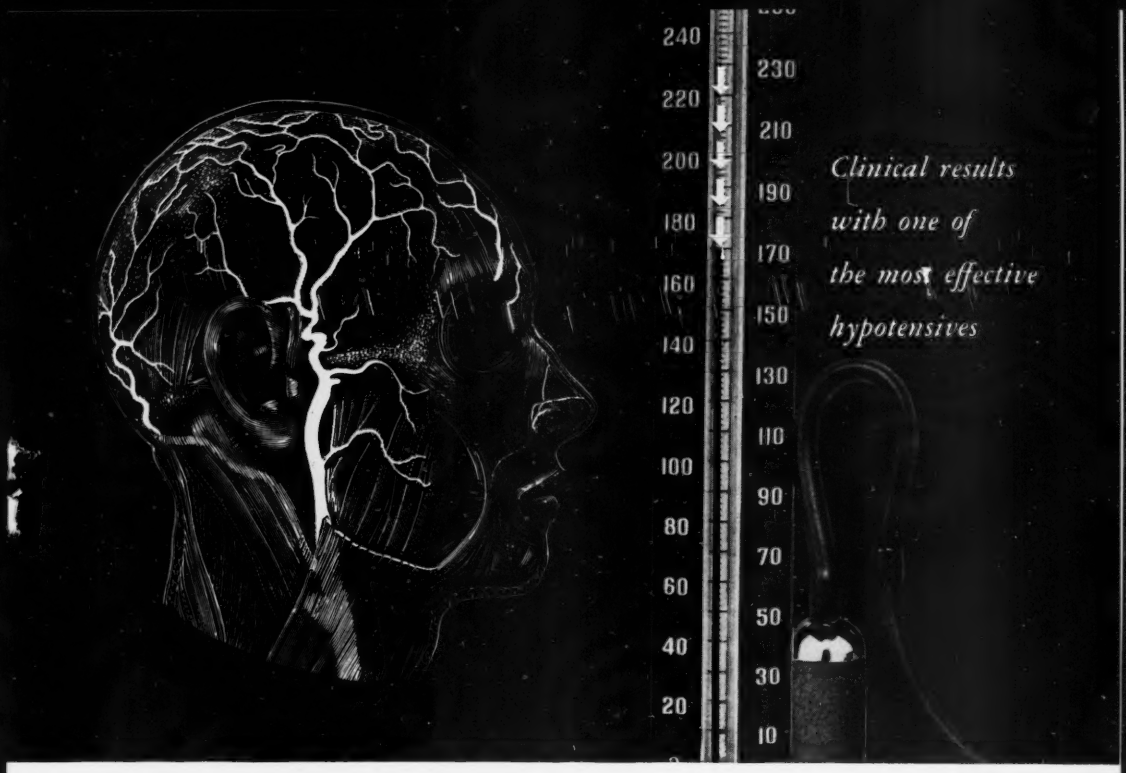

Improvement in 79% of patients with hypertensive headache[1]

In addition to the desired reductions in excessive blood pressure in an average of 80 per cent of patients,[1,2] Methium therapy may result in striking relief of the ominous and disabling headaches common to hypertension.[1] For example, headache was relieved in 30 of 38 patients in one study involving 120 hexamethonium-treated patients.[1]

With continued management, up to or beyond a year, blood pressure has been reduced and stabilized, and cardinal symptoms arrested or reversed, without any increase in dosage.[1]

As blood pressure is reduced, and even without reduction, hypertension symptoms have regressed. Retinopathy may disappear; headache, cardiac failure and kidney function may improve.

Methium, a potent autonomic ganglionic blocking agent, reduces blood pressure by interrupting nerve impulses responsible for vasoconstriction. Because of its potency, careful use is required. Pretreatment patient-evaluation should be thorough. Special care is needed in impaired renal function, coronary disease and existing or threatened cerebral vascular accidents.

Literature and samples will be sent promptly if requested.

References:

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1. Editorial: The Lancet *266*:350 (Feb. 13) 1954.
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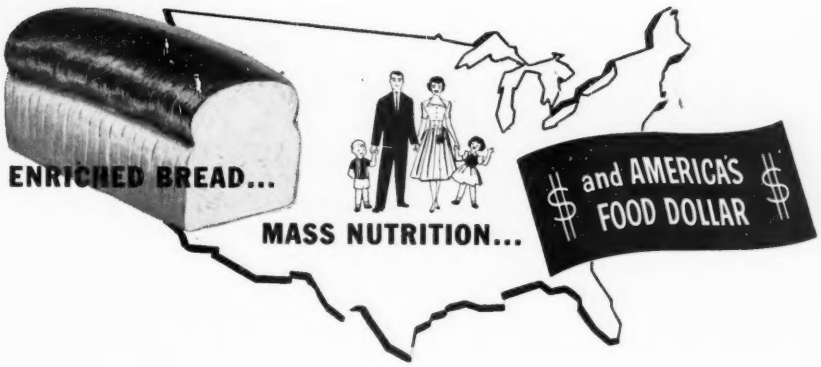

THE nationwide average retail price of 5½ ounces of enriched bread (the estimated average daily consumption) is approximately 5.8 cents.[1] This small fraction of America's food dollar has been responsible for notable gains in mass nutrition and health.[2] The National Research Council and the American Medical Association's Council on Foods and Nutrition have recently reaffirmed their endorsement of the enrichment of bread in the light of "good evidence that enriched bread has been beneficial to the public."[3]

Column I of the appended table shows the amounts of nutrients and nutrient energy provided by 5½ ounces of enriched bread. Column II gives the percentages of the recommended daily dietary allowance[4] available from this amount of enriched bread.

CONTRIBUTION OF 5½ OUNCES OF ENRICHED BREAD

	Nutrients and Calories	Percentages of Allowances (1953)[4]
Protein	13.2 Gm.	20%
Thiamine	0.37 mg.	26%
Niacin	3.4 mg.	24%
Riboflavin	0.23 mg.	14%
Iron	4.1 mg.	34%
Calcium (average)	137 mg.	17%
Calories	418	14%

It is evident that enriched bread furnishes substantially more than its share of most nutrients. Thus it compensates for deficiencies of these nutrients in other foods of the everyday diet. Since virtually all enriched bread is made with nonfat milk solids, its protein—containing an average of 10.5 per cent milk protein and 89.5 per cent wheat and yeast proteins[5]—functions for growth as well as tissue maintenance.

Enriched bread might well be considered a basic food in maintaining the high nutritional status of the American people, yet it can be purchased for so small a percentage of the American food dollar.

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The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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